THE INFLUENCE OF HUMAN CORE TEMPERATURE ON MINUTE VENTILATION

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By

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Abstract

Body temperature is known to affect human ventilation ($\dot{V}_E$), yet the nature and mechanisms of this relationship are not resolved. The first study in this thesis explores how exercise-induced increases in body temperature affects ventilatory components, namely tidal volume (V_T) and frequency of respiration (f), and if these relationships are reproducible. Expressed as a function of esophageal temperature (T_{es}) in seven adult males during incremental exercise to maximum, ventilation and its components were reproducible using intraclass correlation coefficients, $0.84 < R < 0.93$ ($p<0.05$). Since the relationships between ventilation variables and T_{es} were reproducible, a second study examined whether the mechanism of this effect could be mediated by an increased ventilatory sensitivity to CO_2. Central sensitivity to CO_2 was assessed using a modified Read rebreathing protocol before and after exercise induced warming in 6 male subjects. The slope and threshold point of ventilation expressed as a function of end tidal carbon dioxide were increased and decreased respectively, indicating an increased to sensitivity to CO_2 after body warming. In conclusion, the results support

core temperature influence on human ventilation in a reproducible manner and that the effect of ventilation may be partially mediated by an increased central sensitivity to carbon dioxide.

Acknowledgements

Thank you for the dedicated assistance of Dr. Matthew White and the unwavering support of my family and friends.

I am treating you as my friend asking you share my present minuses in the hope I can ask you to share my future pluses.

-- Katherine Mansfield

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List of Abbreviations and Symbols

ATP – Adenosine Triphosphate

CBD – Carotid Body Deneverated

CNS – Central Nervous System

CO_2 – Carbon Dioxide

DRG – Dorsal Respiratory Group

f – Frequency of Respiration

$[H^+]$ – Concentration of Hydrogen Ions

HND – Hilar Nerve Denervated

HVD – Hypoxic Ventilatory Decline

LA – Lactic Acid

MBC - Maximum Breathing Capacity

O_2 - Oxygen

PA_{CO_2} – Partial Pressure of Alveolar Carbon Dioxide

PA_{O_2} – Partial Pressure of Alveolar Oxygen

Pa_{CO_2} – Partial Pressure of Arterial Carbon Dioxide

Pa_{O_2} – Partial Pressure of Arterial Oxygen

$P_{ET}CO_2$ – Partial Pressure of End-Tidal Carbon Dioxide (kPa)

pHi - pH of Intracellular Fluid

^{31}P-MRS – ^{31}P-Magnetic Resonance Spectroscopy

R – Respiratory Quotient ($\dot{V}O_2/\dot{V}CO_2$)

SBC – Selective Brain Cooling

SD – Significant Difference

SE – Standard Error

T_{CR} – Cribriform Plate

T_{es} – Esophageal Temperature (°C)

$\dot{V}CO_2$ – Rate of Carbon Dioxide Production

$\dot{V}_E$ – Ventilation ($L \cdot min^{-1}$)

$\dot{V}_E/\dot{V}O_2$ – Ventilatory Equivalent for Oxygen

$\dot{V}_E/\dot{V}CO_2$ – Ventilatory Equivalent for Carbon Dioxide

$\dot{V}O_2$ – Rate of Oxygen Consumption

VRG – Ventral Respiratory Group

V_T – Tidal Volume

VT_1- First Ventilatory Threshold

VT_2 – Second Ventilatory Threshold

List of Definitions

Carbon Dioxide Sensitivity – This number refers to the slope of the ventilation versus partial pressure of end tidal carbon dioxide curve. A higher sensitivity refers to a larger slope (δrise/δrun).

Group IV Afferents – Afferent mammalian nerve fibers involved in reflex responses with small diameter (0.7 – 1.2 μm) and low conduction velocities (0.5-2.0m/s); also called Dorsal Root C fibers.

Hilar Nerve – Is pulmonary branch of the vagal nerve in the horse/pony.

Plateau Point – This is a distinct point on a curve where the slope (δrise/δrun) changes from a positive number to a value close to or equal to zero in a relatively short period of time.

Resection – A procedure performed for the specific purpose of removal, e.g. carotid body resection involves the removal of the carotid bodies.

Threshold Point – This is a distinct point on a curve where the slope (δrise/δrun) changes from a value close to or equal to zero to a relatively high positive number.

Introduction

Background of Study

The study of the control of ventilation during exercise has received considerable attention in the scientific literature (7, 14), however, no single theory seems to fully account for the entire increase in ventilation ($\dot{V}_E$) which accompanies incremental exercise. Many researchers have demonstrated that an increased core body temperature is linked to the control of ventilation, during both passively induced body warming (1-3, 5, 6, 8, 11, 13) and actively induced body warming (15, 16). Hence body temperature could be one of the factors that leads to the hyperpnea which accompanies exercise. Relative to other potential mediators of exercise-induced changes in ventilation (7), body temperatures have received considerably less study. Thus it remains to be established how body temperature changes during exercise are related to exercise induced changes in ventilation.

Overview of Study

This main purpose of this thesis is to investigate the relationship between body temperature and ventilation ($\dot{V}_E$). Chapter 2 is a review of the

literature pertaining to the regulation of body temperature, the control of ventilation and the way in which both control systems interact with each other.

White and Cabanac (16) used a cycle ergometer to increase the core body temperature of six trained males. They observed core temperature thresholds for the ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$) and the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$), which would suggest that the hyperpnea displayed by humans at the ventilatory threshold may be partly due to core temperature. Chapter 3 is a study of the reproducibility of these thresholds. As well, the study in chapter 3 investigated if such thresholds also exist for tidal volume (V_T) and the ventilatory frequency (f), and if present, whether or not these thresholds were reproducible.

One of the ways body temperature is hypothesized to influence $\dot{V}_E$ is by affecting the ventilatory response to CO_2 (1, 4-6, 10). Researchers have found that increasing core temperature increases the sensitivity and/or decreases the partial pressure of end tidal CO_2 ($P_{ET}CO_2$) threshold point at which $\dot{V}_E$ starts to increase rapidly (1, 4-6, 10). Chapter 4 investigates how $\dot{V}_E$

responds to increasing levels of $P_{ET}CO_2$ at normo- and hyperthermia. The difference between this and previous studies in this area is the combined use of esophageal temperatures as an indicator of core temperature, the use of breath-by-breath analysis for assessment of ventilation and exercise-induced body warming.

Esophageal temperature has been shown to be a good indicator of core body temperature whereas rectal temperature is a slow responding representation of core temperature (9). In addition properly positioned tympanic temperature thermocouple is an excellent measure of core temperature. The more recently developed hand-held infrared tympanic thermometers have been shown to be an unstable with poor reproducibility (12).

Breath-by-breath analysis gives a greater precision for assessment of changes in ventilation than does non-breath-by-breath indirect calorimetry, since the results are being collected at a rate closer to real time. Attributes of interest such as thresholds, and slopes are more precisely identified with this method of data collection.

Exercise-induced body warming gives this study better external validity when trying to establish the reasons for exercise hyperpnea.

Compounding factors that are inherent with exercise may be integral for the ventilatory response to hyperthemia.

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Review of Literature

Human Temperature Regulation

Introduction

In humans and other mammals body temperature must be controlled with considerable precision to allow normal function of the body's physiological and metabolic systems. The control system for human body temperature is yet to be completely resolved (8). Animals need a way to sense temperature, since a deviation from optimal conditions requires compensatory measures to maintain a constant internal body temperature. Sensing is performed by temperature sensitive neurons (34) or thermoreceptors.

The signals from these thermoreceptors must then be analyzed to determine if-and-what thermoregulatory response is necessary (8). The weight that the control system places on each input and the thermoregulatory responses it initiates in response to particular inputs is not clear (9).

The identified mechanisms of thermoregulation include neural, chemical and behavioral components. The effectors of these mechanisms include peripheral vasomotor tone, blood distribution, sweating, shivering, ventilation, non-shivering thermogenesis and adjusting the environment (i.e.

behavior). These effectors enable heat loss and/or heat gain by either radiation, convection, conduction, evaporation or chemical processes (8).

Thermoreceptors

In humans, thermoreceptors are located both centrally and peripherally in the body although this distinction is arbitrary since thermoreceptors are evident at most tissue levels (8). The main receptors of the central nervous system (CNS) are thought to be in the hypothalamus but other CNS sites have been found in the spinal cord and the medulla (8). Heating or cooling these areas causes a compensating thermoregulatory response (9). How these sites may interact with each other is not completely resolved (8).

Peripheral thermoreceptors can be located in the skin and these receptors have been shown to regulate temperature since their activation, with an isothermal core, elicits appropriate thermoregulatory responses (9).

Sensing temperature appears to involve two different types of thermoreceptors, cold and warm receptors. For both classes of thermoreceptors their firing frequency is a non-linear function of their ambient temperature. If body temperature is decreased from optimal

conditions the activity of the warm receptors decreases to a minimum and the activity of the cold receptors increases to a maximum, subsequent decreases in body temperature causes a decrease in the activation of the cold receptors. As temperature is increased above resting levels, the frequency of the cold receptors decreases to a minimum and the activity of the warm receptors increases to a maximum. Subsequent increases in body temperatures cause a reduction in frequency of the warm receptors (34).

Regulation of Body Temperature

As the temperature at these thermosensitive sites drops below a lower threshold, vasoconstriction, metabolic rate, and shivering takes place in an effort to increase heat production. As body temperature increases above an upper boundary, sweating and/or panting and vasodilation occur and progressively increase in proportion with further increases in body temperature (8). While keeping the skin temperature constant, the range of core body temperatures between the upper threshold, indicating the onset of sweating, and the lower threshold, indicating the onset of shivering, has been proposed as the 'null zone' (54). The core temperature set-points for the onset of sweating and for shivering is altered by skin temperature. A higher

skin temperature would cause the set-point for sweating and for shivering to lower, and a lower skin temperature would cause the set-point for sweating and shivering to increase (7, 54).

Thermoregulatory Effectors

Peripheral Blood Distribution

When the core body temperature is in the proposed null zone, there are periodic fluctuations in cutaneous blood flow due to peripheral vasodilation and peripheral vasoconstriction. As ambient temperature increases, there is an increase in the proportion of vasodilation to vasoconstriction. During lower ambient temperatures, there is an increase in the time period of peripheral vasoconstriction. The magnitude of these changes is dependent on the ambient temperature (8). Thus the body is capable of controlling, to some extent, the amount of heat lost through thermal radiation (60).

In addition, venous blood can return to the core in vessels that are adjacent to arteries or in veins that are located at a distance from arteries. During cold stress, blood is diverted into veins that are running close to the arteries, the resulting countercurrent heat exchange warms the blood

entering the core and cools the blood entering the appendages, preventing warm blood from reaching areas where there is a high surface area to volume ratio (1); hence, this prevents appendages from acting like a thermal radiator. During heat stress the opposite response occurs, blood is diverted into veins that are not close to the arteries (8) so less countercurrent heat exchange occurs (1). The result is that the skin is at a temperature close to the core temperature, promoting radiation (8).

The mechanism for vasoconstriction is known to be due to the sympathetic release of noradrenaline (42). The mechanisms involved in vasodilatation is not as clear (41). In response to heat there is an initial dilation that occurs due to the removal of sympathetic vasoconstrictor tone (42, 63) and this has been labeled as passive vasodilatation (41). However, vasodilatation exceeds the passively achieved blood flow increase, which would indicate that some active mechanism is present resulting in active vasodilatation (41). One possible substance that may cause (72) or be partly responsible for active vasodilation (26) is nitrous oxide. Another possibility is that vasodilatation is enabled by a cotransmitter released by sympathetic cholinergic nerves (43). Since atropine partially blocks this active

vasodilation acetylcholine and an unidentified co-transmitter are thought to mediate this response (41).

Sweating

The conversion of a liquid to a gas involves a change of state, and hence requires energy in the form of heat. The quantity of this energy is known as the latent heat of vaporization. Liquid released onto the surface of the epidermis will absorb heat from the body to undergo this phase change, effectively removing heat energy from the body. In humans, ecrine sweat glands are cholinergically innervated and are activated during high core temperatures and during exercise (8).

Shivering

Catabolism of Adenosine Tri-phosphate (ATP) molecules is an inefficient process (2), this inefficiency enables excess energy to be released as heat, thus warming occurs. Efficiency is defined as the amount of work done divided by the total energy expended (29), large muscle activities such as walking are typically 25% efficient (28). Shivering is a rhythmic

asynchronous contraction of skeletal muscles, the asynchronous nature prevents work from being done, but the increased muscle activity brings about an increase in the rate of ATP use and heat production (10).

Non-shivering Thermogenesis

Some mammals and young humans have cells which are capable of increasing energy expenditure. An uncoupling mechanism dissociates the main process of ATP production from the catabolism of food by shunting hydrogen ions across the inner mitochondrial membrane, hence the hydrogen ion gradient created by the electron transport chain is not converted into chemical energy (ATP). The result is an increase in heat production in a manner that is not coupled with work, allowing energy reserves to be used for the sole purpose of heat production (37). The main tissue type thought to be responsible for this method of thermogenesis is brown adipose tissue (36), although more recent work shows several other tissues in which heat production is influenced by uncoupling proteins (22).

Ventilation

Increased ventilation of the upper airways is also a potential thermoregulatory heat loss effector (8, 12, 46, 61, 84). Rasch and colleagues (61) found the total heat loss from the head and the respiratory tract to be 200 to 250 W at a workload of 150 W. This is a substantial fraction of the total heat generated in the body at this workload, which was estimated to be about 520 W. Rasch's study illustrated the importance of respiratory heat loss in human total body heat balance.

The effects of body temperature on ventilation in humans are the crux of this literature review. Consequently a review of the current literature pertaining to the control of ventilation ensues. Following that assessment is a review of how temperature plays a role in this control. The possibility of ventilation as a thermoregulatory response brings about the question of how body core temperature affects ventilation and through which mechanisms this occurs.

Ventilatory Response Pattern During Submaximal Exercise

Ventilation ($\dot{V}_E$) expressed as a function of exercise intensity during moderate, submaximal, exercise has been shown to have either a biphasic or triphasic response to exercise. There is an initial surge in ventilation that begins with the onset of exercise (20) which may be independent of the work rate (82). The first response is subsequently replaced by a period of a slower rate of increase (phase 2). The second phase may be signaled by an altered gas composition in the mixed venous blood and increasing rates of oxygen and carbon dioxide flow in the alveoli. The third phase is thought to be the sum of the first two phases (82) and is a steady-state level (74). At higher intensities the phase 1 response is a lower percentage of the phase 3 $\dot{V}_E$ and phase 2 has a longer time period (74).

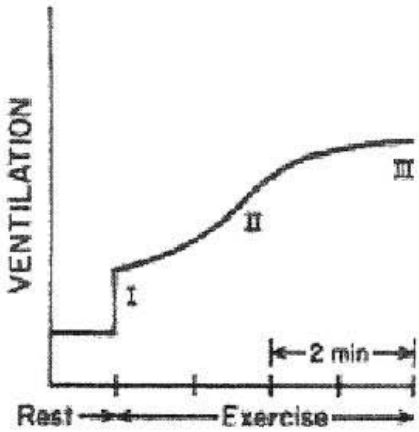

Figure 2.1 Ventilation at rest and during sub-maximal exercise expressed as a function of exercise intensity or oxygen consumption. Figure obtained from Wasserman (4).

Ventilatory Response Pattern During Incremental Exercise

In progressively more difficult or incremental exercise the increase in ventilation is initially accounted for by an increase in tidal volume (V_T). Once a V_T plateau is reached the increase in ventilation becomes due to an increase in frequency of respiration (f) (35, 48). This change in $\dot{V}_E$ component behavior typically occurs at about half of the vital capacity (35, 48). Ventilation increases as a function of the rate of oxygen consumption,

after passing the anaerobic threshold $\dot{V}_E$ begins to increase at a faster rate despite a steadily increasing in work rate.

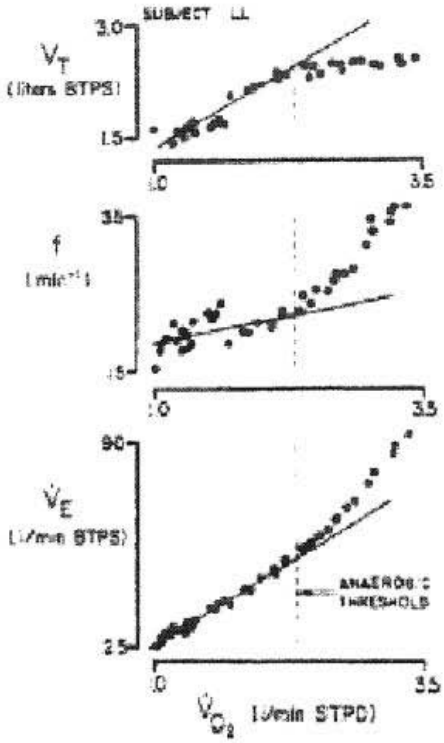

Figure 2.2. Tidal Volume (V_T) and frequency of respiration (f) and ventilation expressed as a function of oxygen consumption during incremental exercise to the point of exhaustion. Indicated in the figure are VO_2 thresholds for the V_T plateau, the onset of elevated f and the 'ventilatory' break point. Figure obtained from Martin and colleagues (7).

Potential Metabolic Factors Influencing Ventilation During Exercise

Carbon Dioxide and Exercise Ventilation

Arterial Carbon Dioxide Partial Pressure

The arterial partial pressure of carbon dioxide (Pa_{CO_2}) is known to be responsible for the control of the respiratory system at rest (68, 79). Low levels of Pa_{CO_2} attenuate ventilation and high levels of Pa_{CO_2} accentuate ventilation. Approximately 80% of the resting ventilatory response is mediated by the central respiratory control center and 20% of the response is mediated by the peripheral chemoreceptors (79). However, the involvement of Pa_{CO_2} in the control of ventilation during exercise is questionable. Both non-human and human studies have focused on the influence of Pa_{CO_2} on changes in ventilation during exercise

Non-Human Studies of Pa_{CO_2} and Exercise Ventilation

In ponies studied at various steady state treadmill workloads, the Pa_{CO_2} has been shown to decrease maximally during the first 30-60 s of exercise (27) or in the first 90 s (59) this initial decrease in Pa_{CO_2} was followed by a

slower progressive decrease or a steady state (27, 59). The decrease in Pa_{CO_2} was observed to have a direct inverse relationship to the rate of oxygen consumption (27). In goats and other mammals, the levels of Pa_{CO_2} during exercise are similar to levels at rest (56). Mitchell (56) believes that the mechanisms responsible for controlling ventilation act in a way so as to maintain resting levels of Pa_{CO_2}, since the ratio of the rate of inspiration to the rate of carbon dioxide production changes in a manner that maintains a constant level of arterial CO_2. The results support the hypothesis that in non-human mammals either, Pa_{CO_2} does not account for the large increase in $\dot{V}_E$ observed during exercise or that the sensitivity to CO_2 is increased during exercise due to other factors such as temperature.

Human Studies of Pa_{CO_2} and Ventilation

During incremental exercise to maximum in humans, the arterial level of carbon dioxide has also been shown to be maintained or move in a direction opposite to that which would increase resting ventilation (32, 52). Ventilation increases linearly with carbon dioxide production, maintaining isocapnia or over compensates for the increased carbon dioxide production

to produce a slight hypocapnia. Again, arterial carbon dioxide would appear not to be a mechanism of control of ventilation since Pa_{CO_2} does not increase despite an increased $\dot{V}_E$, or the sensitivity to carbon dioxide increases with exercise due to other factors that are affected by exercise and the resulting increased sensitivity increases $\dot{V}_E$ with no change in Pa_{CO_2}.

Carbon Dioxide Flow Rate and Ventilation

Carbon dioxide flow rate is the amount of carbon dioxide that flows to, or across the lungs. Some investigators suggest that increased CO_2 flow to the lung is the sole mechanism for the exercise induced increase in ventilation (21, 76). This view supports that if CO_2 flow rate to the lung is a mediator of ventilation, then changing the CO_2 flow should give proportionate changes in $\dot{V}_E$. Again both human and non-human studies have examined the role of CO_2 flow rate and the control of ventilation.

Non-human Studies of Carbon Dioxide Flow rate and Ventilation

To experimentally increase the CO_2 flow rate to the lung Wasserman (76) chemically increased the cardiac output of dogs. Increasing the heart rate should cause more blood to flow to the lungs thereby increasing the CO_2 flow rate across the lungs. Heart rate was increased with an injection of the β receptor agonist isoproterenol into the superior vena cava in lightly anesthetized dogs. The increase in cardiac output resulted in an increased $\dot{V}_E$ with little or no change in end tidal CO_2 pressure. Removing the tachycardia with β receptor blockers removed this hyperpnea. This ventilatory response to heart rate was termed 'cardiodynamic hyperpnea' and was not affected by removal of the carotid bodies, breathing 100% oxygen or by bilateral cervical vagotomy. Cardiac hyperpnea maintained isocapnia and was attenuated by hypocapnia intiated by mechanical hyperventilation prior to the isoproterenol injection (76). This provides supporting evidence to the CO_2 flow rate theory.

The effects of using venous CO_2 loading to increase CO_2 flow across the lung on ventilation has also been studied by Wasserman et al. (76). The

femoral artery in anaesthetized dogs was cannulated and the blood was passed through a membrane gas exchanger equilibrated with 5% CO_2 in air and returned to the femoral vein on the ipsilateral side. It was found that ventilation changed in a manner such that arterial CO_2 pressure remained constant. The $\dot{V}_E$ increased proportionately to the increase in end tidal CO_2 Pressure (76). Both of Wasserman's studies suggests that the ventilatory drive is tightly coupled with CO_2 flow in the central circulation in dogs, so as to maintain arterial isocapnia. So the results would suggest that in dogs the level of CO_2 in the blood enveloping the lungs gives proportional changes in $\dot{V}_E$.

Human Studies of CO_2 flow rate and Ventilation

Decreasing the flow rate of blood to the lungs in humans, by decreasing the cardiac output with an infusion of β blockers (propranolol) should temporarily decrease the flow rate of CO_2 to the lungs. Wasserman (76) decreased heart rate in this manner and the result was a simultaneous decrease in $\dot{V}_E$ and $\dot{V}CO_2$ production. Ventilation rate and $\dot{V}CO_2$ subsequently returned to preinfusion rates despite an ongoing decreased heart rate,

returning CO_2 flow to normal levels. This decrease in ventilation was attributed to a transient discrepancy between carbon dioxide produced by the tissues and the carbon dioxide flow to the lungs (76). Throughout the protocol there was little increase (average, 0.71 mmHg) or no change in end-tidal CO_2 pressure, suggesting a tight coupling between the rate of CO_2 production and $\dot{V}_E$.

Another attempt to observe the effects of CO_2 flow rate on ventilation was made by Heigenhauser and colleagues (33). The methodology included reducing the muscle glycogen in subjects through repeated maximum exercise and a high fat-protein diet. Heigenhauser theorized that a reduction in muscle glycogen would cause the subjects to rely more on free fatty acids utilization for energy, this would cause a reduction in the R resulting in an associated fall in CO_2 production. The subjects underwent incremental exercise on a cycle ergometer to maximum intensity. Although the methodology failed to reduce the rate of carbon dioxide production, $\dot{V}_E$ for a given work rate was higher on the high fat-protein diet than in control conditions. Since the increase in ventilation was not accompanied by an

increase in CO_2 flow rate in the lungs, the authors concluded that other factors must also serve to modulate $\dot{V}_E$ (33).

So the literature is divided on the CO_2 flow rate hypothesis in humans and although CO_2 flow rate seems to play a role in ventilation it is probably not the sole mechanism for its control since it can only be demonstrated at rest and there are dissociations between CO_2 flow rate to the lungs and ventilation (76). Wasserman's (76) study, however interesting, is still indirect since the changes to ventilation were induced in resting animals. It remains to be demonstrated how CO_2 flow rate during exercise influences ventilation, if at all.

Carbon Dioxide Effects on the Carotid Body

The chemoreceptors in the carotid body are responsible for peripheral control of ventilation in resting subjects. During exercise the possible role of the carotid bodies in the control of ventilation has been examined in a series of studies.

Smith and colleagues (70) found that perfusion of the carotid bodies with hypocapnic blood in the dog served as a powerful inhibitor of ventilation and high levels of carbon dioxide in the perfused blood did not

act as an initiator of hyperventilation (70). Although it is not specifically mentioned, datum from Pan et al. (59) seem to support this notion. Ponies in whom the carotid body was denervated demonstrated a significantly greater hypocapnia then normal ponies during the first 90 seconds of exercise. When the carotid body was removed, carotid body mediated inhibition of $\dot{V}_E$ was also removed and the ponies hyperventilated to a lower Pa_{CO_2}.

However, in goats it was observed that carotid body denervation (CBD) resulted in a resting hypoventilation and an increased Pa_{CO_2}. This is despite the finding that Pa_{CO2} was regulated by the goats with the same precision during rest and exercise as the carotid body intact group (56). In this study the Pa_{CO_2} was observed during exercise in normal and CBD goats, Pa_{CO_2} remained at resting levels during exercise in both groups (56).

So the literature is divided on the affect that CO_2 has on the carotid body and ventilation. The carotid body may inhibit ventilation during hypocapnia (70) or the carotid body may be relatively unimportant since the Pa_{CO_2} was regulated to the same precision in CBD goats (56).

Carbon dioxide effects on the components of ventilation

One method for assessing the effects of CO_2 on ventilation is to see how arterial carbon dioxide affects the tidal volume and frequency of respiration or components of ventilation. A possible link between CO_2 and tidal volume is indicated in work by Martin and Weil (48). During progressive exercise to maximum intensity, humans at some point exhibit a threshold in $\dot{V}_E$ when expressed as a function of $\dot{V}O_2$. This threshold is indicated by a rapid increase in the slope of ventilation relative to work rate or $\dot{V}O_2$. It been shown that in humans preventing the onset of hypocapnia that accompanies the ventilatory threshold increases the point at which the increase in $\dot{V}_E$ switches from being primarily due to V_T to being due to increases in f (48). Hence, for a given $\dot{V}_E$, V_T is greater and f is lower when hypocapnia is prevented by breathing hypercapnic gas, indicating that CO_2 is influencing the components of ventilation during exercise in humans.

Further support for the effect of CO_2 on V_T is given by some researchers who show that the lowered airway CO_2 pressure increases intrafusal stretch receptor activity (67). Intrafusal stretch receptors respond

to changes in muscle length by contracting the muscle where they are located, which indicates that airway hypocapnia can induce the V_T limitation (48). Changes in V_T during carbon dioxide rebreathing (oxygen levels held constant) have been shown to be the same as the changes in tidal volume during exercise (35). The nature of the dependence of V_T on CO_2 and the effects of other factors, such as temperature, on this dependence is an area that requires further work.

Oxygen and Ventilation

Effect of Oxygen on Carotid Bodies and the Components of Ventilation

As mentioned previously, the carotid chemoreceptors are thought by some researchers to have a role in the control of ventilation in response to CO_2 (56, 70). There are also studies which have shown that carotid bodies are influenced by arterial oxygen (38, 44). Mammals normally show a biphasic response to hypoxia. The initial phase involves an increase in $\dot{V}_E$ and the second phase begins after a short period of time (5 minutes for a Pa_{O_2} of 40 – 55 Torr) and involves a steady decline in $\dot{V}_E$ known as the hypoxic

ventilatory decline (HVD), the reasons for the biphasic response is ambiguous (44).

Carotid body denervated cats were compared to intact cats under conditions of hypoxia to establish the effect of oxygen on the carotid bodies (41). The normal cats displayed the typical biphasic response for ventilation that has been observed in both humans and cats. Ventilation initially increased for 5 min to a maximum of about 211% of resting value then decreased to 114% of resting value at 25 min. In carotid body denervated cats there was no response to either isocapnic hypoxia or hypoxia augmented with 2% hypercapnia. This would indicate that the carotid bodies are in some way responsible for the hyperventilation that accompanies hypoxia and may be involved in the HVD that occurs after the initial increase in $\dot{V}_E$ (44). In humans HVD decline did not occur in patients who had undergone carotid body resection 20 y prior to experimentation, suggesting that oxygen influences the carotid bodies and further supporting the theory that the carotid bodies are responsible for HVD (38). It is unknown what secondary compensations that these resectioned patients may have adopted.

Increases in ventilation due to hypoxia in the carotid body were shown in female dogs at rest to be entirely the result of an increase in V_T (70). Hypoxia in conjunction with hypocapnia at the carotid body also induces an increase in $\dot{V}_E$ that is entirely due to an increase in V_T, but this increase in $\dot{V}_E$ is substantially lower then hypoxia alone (70). However, other studies have indicated that HVD may not be due to the carotid bodies. In two studies on anesthetized animals, carotid sinus nerve discharges remain elevated during HVD (78) and phrenic nerve activity was depressed during 10 min of sustained hypoxia in anaesthetized, paralyzed, and glocomectomized cats (55). Hence the HVD seems to be caused at a stage later than the afferent (carotid body) and prior to the activation of effector nerve (phrenic nerve) in the neural pathway that is responsible for the control of the muscles affecting ventilation.

Acidity and Ventilation

Evidence to support that hyperventilation in response to heavy exercise is due to the resulting acidosis either in the arteries (24, 81) or in the extracellular fluid bathing the muscle (57). It is reasoned that the increased

metabolic acid production induces a respiratory compensation marked by an increase in $\dot{V}_E$ (24, 77, 81).

Arterial Acidity

Arterial pH has been shown by many researchers to affect ventilation (24, 77, 81). This effect can be either carotid body mediated (3, 77) or carotid body independent (24). The carotid chemoreceptor is thought of as a mediator of the dominant component of acute ventilatory response to metabolic acidosis (24, 77, 81). During exercise there is an increase in the non-metabolic fraction of blood carbon dioxide due to the buffering of lactic acid, this increase in CO_2 may stimulate the carotid body chemoreceptors and cause the exponential or disproportionately large increase in ventilation, relative to the rate of oxygen consumption (75).

Non-human Studies of Arterial Acidity and Ventilation

There is evidence to suggest that the $\dot{V}_E$ response to arterial acidosis is independent of the carotid bodies. To investigate the response to lactic acid Erickson et al, (24) observed the changes in $\dot{V}_E$ that occurred in normal, CBD

and Hilar nerve denervated (HND) ponies during intravenous lactic acid infusion (jugular vein) and treadmill exercise at various intensities. During rest and low intensity exercise in all groups, and during moderate exercise in CBD ponies, there was an increase $P_{a_{CO_2}}$ by about 2 Torr (266.6 Pa) during the first 2 minutes of infusion. Between 2 and 10 min there was significant decrease in $P_{a_{CO_2}}$ of about 5 Torr (666.6 Pa), which was similar for all groups. Ventilation changed after 30 s until about 2 min, after which there was no significant change in $\dot{V}_E$ for all groups at rest or at exercise. For the remainder of the protocol there was no significant difference between all groups. The authors concluded that lactic acid accentuates ventilation at rest and during submaximal exercise in the ponies but the role of the carotid bodies and the Hilar nerve afferents are not critical for this response (24).

In contrast, CBD dogs, which normally hyperventilated in response to lactic acid, failed to hyperventilate in response to lactic acid infusion during rest or exercise (3) supporting the idea that lactic acid mediates control of ventilation by the carotid chemoreceptor. Comparing CBD, hilar nerve denervated (HND), and normal ponies has also demonstrated that

hyperventilation during high intensity exercise is independent of acidosis and the carotid chemoreceptors (59).

Human Studies of Arterial Acidity and Ventilation

The view that there is acid-base involvement in the control of ventilation by the carotid chemoreceptor is supported by data gathered on asthmatic patients with carotid body resection. These individuals were compared to normal subjects during steady state and incremental exercise. The researchers observed that, as expected, resectioned carotid bodies did not affect the initial, abrupt, increase in ventilation (phase II) or the steady state (phase III) response to exercise (Fig 2.1). However, the time course to achieve steady state ventilation (phase II) was significantly slower in the carotid body resected subjects. Above the 'anaerobic threshold' as defined by Wasserman (77), their $\dot{V}_E$ was significantly lower then subjects without carotid body resection (77). This suggests, according to Wasserman (77), that the carotid bodies are responsible for the respiratory compensation for exercise-induced metabolic acidosis but not for the phase I response to

exercise. However, the ongoing pathologies of these patients in the study may have influenced the results (80).

Despite these conclusions, the evidence supports that lactic acid is only partially responsible for the ventilatory responses to exercise. In humans, although it has been accepted by many (19, 77) to use the ventilatory threshold as a non-invasive means of the determination of the point of elevated lactic acid production, this has been brought into question by McLellan (52). The ventilatory response to incremental exercise is argued to include two successive thresholds (53, 56). The initial ventilatory threshold (VT_1) is indicated non-invasively by a continued decrease in the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) and an increase in the ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$). Ventilation increases out of proportion to $\dot{V}O_2$ due to the increased carbon dioxide production resulting from lactic acid (LA) buffering or the non-metabolic increase in CO_2 levels. Buffering of LA increases arterial CO_2 according to the following Henderson-Hasselbalch equation:

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^- \quad (1)$$

According to the equation the rise of blood lactic acid (OBLA) during exercise increases H^+ ions concentration. These ions must be buffered by blood bicarbonate. This causes the above equilibrium to shift to the left (LeChatalier's principle) resulting in an increase in alveolar CO_2 and hence an increased CO_2 flow to the lung. The arterial CO_2 subsequently remains constant (i.e. this is an isocapnic buffering period) since this buffering of the excess carbon dioxide is precisely matched with an increase in $\dot{V}_E$, which is why the $\dot{V}_E/\dot{V}CO_2$ decreases. This first threshold (VT_1) is defined as the "anaerobic" threshold since it is the buffering of the excess lactic acid production which causes the increased $\dot{V}_E$ (52). The second ventilatory threshold (VT_2) is indicated by an increase in $\dot{V}_E/\dot{V}CO_2$ and hence, a fall in Pa_{CO_2}. The mechanism involved for the hyperpnea at higher $\dot{V}O_2$ or workloads is not fully understood, and McLellan believes it to be of neural origin (53).

Further support for two separate ventilatory thresholds was given when the hyperventilatory threshold during progressive exercise was dissociated from the anaerobic threshold indicated by a sudden increase in

lactic acid (31, 33, 40) in subjects in whom lactic acid production was altered by dietary manipulation (glycogen depletion causes a decrease in R). McLellan's (52) work is also supported by Simon et al. (69) who showed that that the ventilatory threshold (VT_2) and the anaerobic threshold (VT_1) occur at different levels of $\dot{V}O_2$ and power output.

Subjects with McArdle's disease hyperventilate during exercise (32), even though they are incapable of increasing arterial lactate and H^+ concentrations. These subjects lack muscle phosphorylase and, hence, are incapable of producing lactic acid. As a result some researchers have used these individuals as a method of studying the extent to which lactic acid affects ventilation. Hagberg (1982) found that McArdle's disease patients still had a hyperventilatory response to exercise and the abrupt increase in ventilation, VT_2, which, during incremental exercise occurs, occurred at a percent of maximum $\dot{V}O_2$ (75-80%) that was not significantly different from the percent of maximum $\dot{V}O_2$ at which VT_2 occurred in normal subjects (32). Based on these results, Hagberg concluded that nonhumoral mechanisms are the most likely cause of hyperventilation.

Hagberg's (32) result was criticized by Whipp (81) who argued that the hyperventilatory response to exercise could be attributed to the pain associated with exercising with McArdles's disease (81). Hagberg (32) countered that only two of the subjects experienced mild pain, and the pain was not experienced until after hyperventilation had occurred (81). McLellan (52) believes that since Hagberg (32) used a ventilatory threshold (VT_2) instead of an anaerobic threshold (VT_1), the conclusion that, the data from the McArdle's patients support a coincidental, not a cause and effect, relationship between lactic acid and ventilation, is unjustified (52). McLellan (52) suggests that Hagberg's (32) data support the theory that carbon dioxide production is the mediator of ventilation below 80% of maximum oxygen consumption and that above 80% the mechanism of control may be neural (52).

Further evidence against lactic acid as an initiator of hyperventilation comes from a study on eight healthy males undergoing incremental exercise at two different intensities until a peak $\dot{V}O_2$ was reached. One test, which was conducted at 60 revolutions per minute, used a standard power output step increment of 60 W every 3 min (SI). The second test was conducted at 90

revolutions per minute and used a higher power output step increment of 90 W every 3 min (HI). As previously shown, the subjects demonstrated a similar relationship between oxygen uptake ($\dot{V}O_2$) and $\dot{V}_E$ and between $\dot{V}_E$ and carbon dioxide production ($\dot{V}CO_2$) at both exercise intensities. However, the results demonstrated that there was a dissociation between blood lactate concentration and ventilation for incremental stationary cycling. Blood lactate accumulation was lower for graded exercise at HI compared to SI. Blood lactate was related to the rate of power output and not to $\dot{V}_E$, while ventilation was related to $\dot{V}O_2$ and $\dot{V}CO_2$ (73). The results do not support the hypothesis that $\dot{V}_E$ changes coincide with changes in blood LA.

In conclusion, the literature is clearly divided on the effects of arterial acidity on $\dot{V}_E$. Some researchers believe acidity is involved in the control of $\dot{V}_E$ by its effect on the carotid body (77). Others believe that arterial acidity does not influence the $\dot{V}_E$ threshold (31, 33, 40). Evidence exists to support the independence of $\dot{V}_E$ from arterial acidity (32, 73). More complicated interpretations also exist as McLellan (52) suggests: the mechanisms may be

metabolic before the anaerobic threshold, and neural after. Clearly more research needs to be done in this area to elucidate how arterial acidity and ventilation are related during exercise.

Extracellular Fluid Acidity

Ventilation is thought to be increased by various metabolites in the extracellular fluid such as potassium (85) and hydrogen ions (25, 64). The pH of the extracellular fluid is thought to increase ventilation (65) by stimulating group-IV afferents (25, 64).

It is difficult to measure the hydrogen ion concentration of extracellular fluid without affecting the muscle. Instead, the pH of intracellular fluid (pHi) can be estimated non-invasively using ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS). A marker (phenylphosphonic acid) is added to the extracellular space and reacts with hydrogen ions, the product has a distinct resonance peak in the Nuclear Magnetic Resonance (NMR) spectrum. Hydrogen ion concentration of intracellular fluid is known to be a good indicator of the pH of extracellular fluid (25), as such, pHi levels are used as an indication of the pH bathing the group-IV afferents. The pH of

the extracellular fluid in muscle is linked to ventilation (25, 64, 65) hence, pHi is also linked to ventilation. Oelberg (57) concluded that skeletal muscle hydrogen ion in the extracellular fluid contributes to the exercise-induced ventilatory response. Oelberg found evidence of this when a subject's ventilation was found to vary linearly with the pHi in the vastus medialis, and did not change in parallel with changes in arterial pH (57). Wasserman (76) argues against Oelberg's theory. He argues that a chemically-induced decrease in heart rate should concentrate metabolites known to stimulate ventilation in the proximity of the group-IV afferent receptors. However, his results showed that a chemically induced decrease in cardiac output actually reduced ventilation (76). As such, despite accumulation of metabolites in the proximity of the group-IV afferent receptors, $\dot{V}_E$ decreased in Wasserman's study.

Although it appears that the pH of the extracellular fluid and the arterial pH may play a role in the regulation of ventilation, it seems unlikely that they are the sole factors in the control of ventilation during exercise.

Neural Responses

Many researchers believe that ventilatory responses are not based purely on metabolites, but also consists of a neural component. The neural components thought to influence ventilation during exercise are divided into behavioral, limb movement, hypothalamic, and thermal.

Behavioral

The first phase of the ventilatory response to exercise (81) is hypothesized to be due to a behavioral component (6), sensory cues initiating increased ventilation based on past experience. This phase typically lasts about 15 –30 s (81). In order to study the immediate changes in V_T and f, Beaver and Wasserman studied blindfolded men (to remove any visual cues) using random intermittent exercise-and-rest periods. Exercise was initiated in response to verbal command from researchers in a random fashion so as to remove anticipatory reactions. The results demonstrated that there was an instantaneous change in f and V_T when exercise began before any change in metabolites had occurred. The respiratory frequency generally increased and V_T was variable but generally decreased immediately with the onset of exercise. Beaver and Wasserman believe the variability in the

responses indicates a learned response and not a fundamental physiological mechanism (6).

Limb Movement

Limb movement changes rapidly with the onset of exercise. Therefore it has been hypothesized to have a neurally mediated effect on ventilation (6, 11, 20, 58). Forster (27) designed a study to investigate this phenomena in the pony. The objective of the study was to determine whether changes in limb movement affected Pa_{CO_2}. The ponies performed incremental tests with varying speed, grades and step frequencies, and exercised with either four limbs or two limbs. It was concluded that the decrease in Pa_{CO_2} brought about by exercise-induced hyperventilation was not influenced by the frequency of limb movement or the number of limbs involved in the exercise. Hence limb movements appear not to be an initiator of ventilation, or as mentioned in the next section, it may be related to ventilation in a manner that is not cause and effect.

Neural Activation of Ventilation from the Hypothalamus

Work by Eldridge and colleagues (23) on unanesthetized decorticate cats has given evidence that parallel neural signals from the locomotor region of the hypothalamus are primarily responsible for locomotory, respiratory, and some cardiovascular responses to exercise. Decorticated cats had their vagus and carotid sinus nerves sectioned. Cats were able to walk spontaneously when suspended over a free-running treadmill, respiratory activity was measured by measuring the electrical activity in a phrenic nerve root, and skeletal muscle activity was measured with electrodes placed in the quadriceps. Treadmill activity was immediately accompanied by an increased respiration and arterial pressure, without a concurrent increase in end-tidal CO_2 tension. When activity ceased a rapid decrease in V_T and f was observed and this supports the hypothesis that ventilation is induced by a pathway which is also involved in locomotion. Furthermore, feedback mechanisms from muscle activity were shown not to be necessary in this response, since rendering the cats paralyzed with gallamamine triethiodide produced the same results as nonparalyzed cats (23). Hence, in cats, it appears that there is a strong neural influence from the hypothalamus, which

initiates both locomotion and cardiovascular responses as well as $\dot{V}_E$ changes in a parallel fashion. How the other initiators of ventilation such as metabolites, behavior, and temperature combine with this response is still in question.

Body Temperature and Ventilation

Body temperature, sensed by thermoreceptors, is believed by some researchers to be a variable which has a relationship with exercise-induced hyperventilation. Passive heating of human core temperatures by 2˚C in a water bath has been shown to increase pulmonary ventilation by 49% (5, 66), oxygen consumption by 19% (66), to decrease end-tidal carbon dioxide tension by 17% (66) or by an average of 4.8 mmHg (5) and to induce a 16% increase in carbon dioxide production (66). Since the temperature-induced increases in $\dot{V}_E$ were out of proportion with metabolic needs, this supports that body temperature may be an independent stimulus to ventilation. Measurements of subjects for Saxton's experiments (66) were done in a thermoneutral environment and during passively (heat chamber) induced hyperthermia (Tympanic temperature, 39.0 – 39.5˚C). The changes in

metabolic rate were suggested to be due to an increase in the basal metabolic rate and not due to 'arousal activities' (66). This conclusion was inferred since the increased work due to hyperpnoea at rest only 'cost's' 0.35 ml of oxygen per liter increase in $\dot{V}_E$ (13) and the cost of sweating only account for a minuscule part of the overall rate of oxygen consumption (66). Saxton's datum also suggests that there is an increased sensitivity to CO_2 with raised body temperature, which supports later studies by Cunningham and O'Riordan in passively heated humans (18).

Other researchers have found that passive heating of humans in a hot water bath caused a significant increase in $\dot{V}_E$ (4, 12, 15). This increase in ventilation was not accompanied by an increase in f and no significant increase in $\dot{V}O_2$ (12, 15). These results suggest that the hyperthermia induced hyperpnea is not due to increased metabolic requirement but may be a vestigal panting response (12). This hyperthermic hyperpnea was demonstrated by Cabanac and White (12) to follow distinct core temperature thresholds for ventilation (12). Choukroun (15) also showed that increasing water bath temperature caused a decrease in vital capacity and a decrease in maximum breathing capacity (MBC). However, the hydrostatic effects of

water have been shown to decrease expiratory reserve volume, functional residual capacity and vital capacity (15). Changes in either of these volumes may affect their remarks about temperature being the mechanism of change, since the hydrostatic effect may be partly responsible for the observed changes.

In another study (71), subjects exercised with and without an elevation in core temperature. Rectal temperature was passively elevated to approximately 38.5°C in the test condition in a climatic chamber. During the exercise at normo- and hyperthermia, rectal temperature was kept constant through the use of cold water sprayed on the subjects and varying the room humidity. In the exercise session f was higher and V_T was lower, O_2 consumption rate lower, and CO_2 production lower than in the normothermic exercise session (control). Although ventilation was not different between normothermic and hyperthermic subjects, the ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) were greater in hyperthermic subjects. The observed increase in f and decrease in V_T may represent what is left of a panting response in humans, and therefore, could be a form of heat loss (45, 46, 71).

Cotes (16) observed an increase in ventilation with increasing body temperature while arterial PCO_2 was held constant. Rises in body temperature with an increase in arterial PCO_2 were shown to have an additive effect on ventilation (17) thus CO_2 appears to accentuate the ventilatory response to temperature, i.e. CO_2 sensitivity seems to increase with increasing temperature. However Cotes (17) only performed the experiment on one subject, so the results are not generally accepted.

Ventilation has also been argued by some researchers to be a method of thermal regulation in humans (12, 46, 61, 84), thus providing a physiological rationale for a temperature induced hyperpnea in humans. Removal of an upper respiratory bypass in conscious patients has been shown to rapidly lower the temperature between the frontal lobes and the cribriform plate (T_{CR}) by 0.4 - 0.8°C (46). In this study by Mariak and colleagues (46), the intracranial temperature also fell below esophageal temperature, indicating the presence of selective brain cooling (SBC) in post-operative patients (46).

Similar results were obtained in a study by Mariak et al. (45). The researchers examined the relationship between cranial temperatures and

noninvasive measurements of core temperatures. For this study (42), tympanic, esophageal, rectal and 3 to 4 cranial temperatures were simultaneously recorded from five subjects during open brain surgery. The brain temperatures during the protocol decreased and were closely followed by tympanic temperature. Simultaneously, esophageal temperature (T_{es}) rose and was significantly higher than both the cranial and tympanic temperatures supporting that T_{es} does not give the best intracranial temperature index. Further support for this ventilation-induced drop in cranial temperature was found when subjects were asked to breathe intensively for three minutes, T_{CR} was shown to drop by a rate of ≈6°C/h (46). The results support the view that cranial temperatures can be influenced by ventilation.

Selective brain cooling has also been shown to occur in goats (14) and numerous other animals (12). In goats, SBC competes with trunk cooling by controlling the direction of the cooled nasal blood flow. The amount of brain cooling increased significantly with rising cerebral temperature and decreased with rising trunk temperature (14). When brain temperature was clamped at 41°C the intensity of SBC was essentially independent of trunk temperature, suggesting that SBC takes precedence over trunk cooling (14).

The occurance of selective brain cooling in humans seems likely because of the close proximity the roof of the nasal cavity to the floor of the anterior cranial fossa (46). Hence, the majority of inhaled air warming occurs in the upper part of the airways (51). Cabanac and White (12) showed that during passive heating in a water bath, tympanic temperature dropped below esophageal temperature (12). In their study involving the direct simultaneous measurement of tympanic, esophageal, and three cranial temperatures, Mariak and colleagues (45) found that tympanic temperature and esophageal temperature are good indications of overall brain temperature and core temperature respectively (45). Therefore, the previously mentioned SBC appears to be supported in humans.

There is also evidence against the existence of SBC. McFadden (50) believes that the humans are designed in such a way that minimizes heat and water loss to the environment, hence, making respiration a poor means of heat loss. Data on subjects breathing frigid air ($-17.8 \pm 1.8^{\circ}C$) showed that the temperature of the airways falls to levels only a few degrees higher than the air temperatures and that there was no difference in airway temperature between exercise and passively induced hyperthermia (50). McFadden (50)

suggests that these findings illustrate that there is little blood bathing the airways. By thermal mapping of the lungs during inspiration and expiration some researchers believe that the main effect of heat transfer during inspiration is to cool down the airways and that the opposite effect can occur during expiration and heat and water can be reclaimed (49, 50). However, breathing frigid air may have affected the subject's normal responses, and the five min exercise of his protocol may not have been long enough to increase core temperature and initiate thermal control by ventilation.

It is probable that temperature has some effect on ventilation since this has been shown in many studies (4, 16, 18, 39). The mechanism by which temperature affects ventilation is still yet to be properly elucidated. One possible mechanism may be that temperature affects a human's sensitivity to CO_2 (4, 16, 18, 39).

Panting versus Non-Panting Response to Hyperthermia

Strange-Peterson and Vejby-Christensen (71) demonstrated, during exercise, that as a body temperature increased above an extrapolated core temperature threshold of 38°C, an increased frequency of respiration was observed with no significant change in ventilation. Strange-Peterson and

Vejby-Christensen (71) may have failed to see an increase in $\dot{V}_E$ due to an insufficient increase in core temperature. Many researchers have found that a rise of 1.5 – 2°C is required to increase ventilation (12, 66). Martin (47) observed that passive heating and exercise-induced heating produced similar changes in ventilation, as body core temperature (rectal) rose, f increased and V_T fell (47). An observed increase in f with a decrease or no change in V_T could be an indication of a vestigal panting mechanism in humans (47).

Cabanac and White (12) found that a passively induced rise in body temperature above esophageal (38.5°C) and tympanic (38.1°C) temperature thresholds resulted in an increase in $\dot{V}_E$. This result is supported by Gaudio and Abramson (30). The increase was due to an increase in V_T with no significant change in f, thus, the increase in ventilation did not resemble a panting response.

How temperature affects the components of ventilation appears to be still in question (11, 27, 44, 68). It remains to be resolved whether a rise in core temperature increases V_T or f, or both (12).

The relationship between Neural and Metabolic Responses

The presence of both neural and metabolic components of ventilation is almost certain. However, the relationship between these mechanisms is ambiguous. It is not certain if they are purely additive or if the two mechanisms are interrelated.

The main focus of this thesis is to explore the relationship between core body temperature and the components of ventilation. A basis for exploring this relationship is to first establish if these relationships are reproducible. Further research will examine whether there is a relationship between body core temperature and CO_2 sensitivity.

As mentioned previously, Cunningham et al. (1957) observed that a passively raised body temperature (rectal) increased CO_2 sensitivity. Carbon dioxide sensitivity was defined as the slope of the regression line on a graph of ventilation as a dependent variable plotted against alveolar PCO_2. This sensitivity was shown to increase by approximately two fold with hyperthermia. An altered slope suggests that the effects of passive hyperthermia and alveolar pCO_2 are not merely additive (18). Cotes (17) found these factors to be additive, however his experiment was based on only a single subject.

Clark and colleagues (16) studied nine trained athletes at various exercise-induced $\dot{V}O_2$ levels while exposed to 5 different levels of inspired PCO_2 for each exercise level. The researchers found the ventilatory response to carbon dioxide was increased during light exercise ($\dot{V}O_2$, 1.08 l/min) and this accentuated response was reduced with increasing workloads. The results indicated that the chemical and non-chemical components of exercise hyperpnea were not directly additive, since the ventilatory response to hypercapnia at rest and during exercise were not parallel (16).

The effect of passive hyperthermia on carbon dioxide sensitivity was also studied by Baker and colleagues (4). Body temperature (Infrared Tympanic) was elevated by 1.5°C in six male subjects. This hyperthermia was shown to increase ventilation, heart rate, metabolic rate and the sensitivity of the ventilatory response to CO_2. However, the threshold point of the CO_2 response of $\dot{V}_E$ versus $P_{ET}CO_2$ did not change with hyperthermia (4).

The effect of passive hyperthermia on ventilation was also investigated by House and Holmes (39) who performed a Read rebreathing test (62) on four subjects before and after body warming induced by a hot

water bath. Breath-by-breath gas concentrations was analyzed by mass spectrometry. House and Holmes (39) did not observe a decrease in the $P_{ET}CO_2$ threshold or an increase in the slope of the $\dot{V}_E$ as a function of $P_{ET}CO_2$ curve (i.e. CO_2 sensitivity). They did, however, like Baker and colleagues (4), see an additive effect of core temperature on the ventilatory response to CO_2 (39).

Research Hypothesis

It is hypothesized that core temperature is an independent and reproducible stimulus to ventilation during incremental exercise. In addition it is hypothesized that the sensitivity to CO_2 will increase with increases in body temperature during exercise.

Testable Hypotheses

(1) Esophageal temperature thresholds for f and V_T plateau points are reproducible during incremental exercise in similar exercise conditions

(2) Esophageal temperature thresholds for $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ are reproducible during incremental exercise in similar exercise conditions

(3) Carbon dioxide sensitivity during CO_2 rebreathing, as indicated by the slope of the $\dot{V}_E$ versus $P_{ET}CO_2$ relationship, will increase in hyperthermia versus normothermia

(4) Thresholds for the onset of increased $\dot{V}_E$ will be decreased during CO_2 rebreathing in hyperthermia versus normothermia

Significance of Study

As the review of literature has shown, the control of ventilation in humans during exercise and hyperthermia is poorly understood. There are numerous conflicting theories all of which have supporting and conflicting evidence. Some of these theories claim metabolites such as CO_2 (21, 76), and pH (25, 64, 65) as the initiator of ventilation, some theories advocate neural mediation of ventilation in response to stimuli such as temperature (12, 20, 61, 83, 84), and limb movements (6).

Still other theories support a joint neural and metabolic influence on ventilation (52) (4, 18, 39). In addition, there are researchers who are interested in the influence of passive body temperature on ventilation (4, 18, 39) however, the influence of exercise induced body temperature on ventilation is still poorly understood.

This thesis will provide further research on the latter model; the joint effect of metabolic and neural influences on ventilation during exercise induced hyperthermia. The results will be directed towards a better understanding of the control of human ventilation during exercise.

Instrumentation

Breath analysis requires: a mouthpiece, a flow meter, a mixing box, a carbon dioxide analyzer and an oxygen analyzer.

Ventilation Measurement

The subjects breathe through a mouthpiece held in their jaw. From the mouthpiece expirations are directed to the appropriate sensing devices. This either consists of a system of one-way valves, or simply tubes which direct gas towards the O_2 and CO_2 analyzers.

The volume of expired gas must be measured by a pneumotach or flow meter. The flow meter measures how much gas is expelled with each exhalation and, depending on the pneumotach used, it may also measure the rate of expiration. For example the Mass Flow Sensor™ on the Sensormedics VMAX 229c metabolic cart uses gold plated stainless steel wires. The onboard computer senses how much power it must provide to maintain a constant temperature in these wires. The amount of power is proportional to the flow rate of gas over the wires, coupled with time, the mass flow sensor can measure volume, rate, and flow. In systems equipped with a mass flow sensor, detection occurs immediately after the mouthpiece.

In metabolic carts where a compact flow sensing device such as the mass flow sensor is not used, the volume of expiration is determined before mixing the gas by a pneumotach. Flexible Collin's tubing connects the mouthpiece to the pneumotach and the tubes must be between 30 and 50 mm in diameter so that resistance is minimized and so that too much air does not remain in the tubing. For the same reasons the pipe must be as short as is possible without interfering with the experiment. After passing through the mass flow sensor the gas flows into the mixing box. The size of the mixing box must be chosen with care, a large box allows for good mixing but takes

a relatively long time to wash out, whereas a small box has a shorter wash out time but may not mix the gases adequately. The exact size of the box is therefore dependent on the aims of the experiment being conducted, for example if large tidal volumes are part of the experiment then a larger mixing chamber will be preferred. Typically the mixing box size is between 0.005 and 0.015 m^3. The gases are mixed with either a series of baffles or a fan. A fan must be used carefully to prevent gas from being pulled through the respiratory valves.

After being mixed (or after the mass flow sensor) some of the gas is sampled the rest of the gas is expelled to the environment. In the VMAX 229c metabolic cart this sampling rate is 500 ml/min. The room should have adequate ventilation so that the expelled gas does not accumulate in the room and change the inspired gas mixture which could influence the estimation of $\dot{V}O_2$ and $\dot{V}CO_2$. The sampled gas is taken to a carbon dioxide analyzer and an oxygen analyzer.

Metabolic Measurement

Commonly used carbon dioxide analyzers utilize infrared absorption as a basis for measuring the concentration of carbon dioxide in a sample of gas. Carbon dioxide absorbs infrared light over a specific range of wavelengths (2000 nm < λ < 2250 nm), so as infrared light is passed through the sample cell, certain frequencies of light are absorbed. The beam passed through the sample is compared to a reference beam, the amount of absorption in the appropriate wavelengths (corresponding to carbon dioxide) indicates the concentration of carbon dioxide in the sample. A higher proportion of infrared light absorption corresponds to a higher concentration of CO_2 in the sample.

Oxygen analysis can use a solid oxide solution, specifically calcia-zirconia. At high temperatures these solid solutions can act as conductors for oxide ions. Placing the solution in an open circuit and exposing the solution to the sample gas allows the solution to conduct the oxide ions. The resultant voltage carried by the oxide ions is proportional to the concentration of oxygen by a calibration equation. Oxygen concentration can also be determined by taking advantage of oxygen's paramagnetic property. A

diamagnetic bell suspended in a magnetic field rotates proportionally to the concentration of oxygen surrounding it.

A mass spectrometer can also be used to obtain the concentration of any gas. A mass spectrometer can separate ions and hence determine concentration according to their mass to charge ratio. Ions entering a magnetic field recieve a force perpendicular to the direction of propagation. The magnitude of this force is proportional to the charge and velocity of the particle and the strength of the magnetic field. When ions of a specific velocity enter the uniform magnetic field of a mass spectrometer they undergo circular motion due to the perpendicular magnetic force. The radius of this circle is proportional to the mass and charge of the particle.

Knowledge of the concentrations of oxygen and carbon dioxide in addition to the knowledge of flow rate and volume from the flow meter we can determine other useful information such as respiration, exercise and metabolic rate.

Co-Authorship Statement

The papers entitled *Reproducibility of the Relationships between Ventilation and Esophageal Temperature During Hyperthermia in Humans* and

Changes in the Ventilation Response to Carbon Dioxide Following Exercise Induced Hyperthermia in Humans were written in collaboration with Dr. M. D. White.

Topic selection for both projects was a joint effort between both researchers. A possible gap in the existing literature was indicated by Dr. M. D. White. Subsequently, research was completed in the area by Ajay Sancheti to identify specific questions.

Ajay Sancheti completed the protocol, methodology, statistical analysis, subject selection, data collection, and writing. Dr. M. D. White provided advice and editing assistance.

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Reproducibility of the Relationships between Ventilation and Esophageal Temperature During Hyperthermia in Humans

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Introduction

At rest, changes in arterial carbon dioxide are tightly correlated to changes in ventilation (30), however the mechanisms underlying the hyperventilation relative to metabolic need during exercise are poorly understood (6). In heavy exercise, arterial carbon dioxide (CO_2) either decreases or remains at resting levels (12, 21) suggesting a changed role for arterial CO_2 in the control of ventilation during exercise. Several hypotheses on the control of ventilation during exercise have been developed (6). The increased CO_2 flux across the lungs during exercise is suggested to be one important stimulus to ventilation (8, 27), but other possible stimuli to ventilation during exercise are also evident (1, 2, 9, 10, 18, 19, 22, 23, 28, 29). These include that ventilation is influenced by exercise-induced increases in lactate (18, 19, 29), arterial acidity (1, 9, 28), extra-cellular acidity (10, 22) and limb movements (2, 23). The body warming that accompanies exercise is another stimulus known to increase ventilation (13, 32), but this mediator of ventilation has received considerably less study (6).

Since both hot water immersion (3, 13, 17, 24) and exercise-induced body warming (25, 31, 32) induce a hyperventilation relative to metabolic

needs, it appears that body temperature is an independent stimulus to ventilation. During passive and exercise induced body warming, distinct core temperature thresholds for ventilation were identified (3, 31) and subsequent to these thresholds ventilation increases proportionately to body core temperatures (3, 31). For humans rendered hyperthermic by exercise it remains to be determined how the components of ventilation change as a function of core temperature during progressive exercise to maximal attainable levels. It is also not yet known if the relationships between core temperature and each of ventilation, tidal volume (V_T), and frequency of respiration (f) are reproducible in progressive exercise protocols. The purpose of this study was to assess these two questions.

Material and Methods

Seven men between the ages of 18 and 40 (mean age = 24 ± 2.7 years; mean weight 77.4 ± 3.0 kg; mean height 1.77 ± 1.6 m; mean ± SE) participated in the study. During the experiments the subjects wore athletic shorts and a short sleeved athletic shirt. The ambient temperature during the exercise sessions was 22.1 ± 0.3°C. An ethics committee for human

experimentation at Memorial University of Newfoundland approved the experiments and all subjects signed an informed consent prior to participating in the study.

Instrumentation

Esophageal temperature was measured using a pediatric sized thermocouple (~2 mm) inserted a mean of 403 ± 3 mm past the nares, a depth which corresponds to the level of the ventricles (20). Skin temperature was recorded from thermocouples at 3 sites (center of forehead, right upper chest, and right thigh) and values are expressed as the un-weighted mean. The subject breathed from a low resistance mouthpiece fitted with two one-way valves. The inspired air was from the laboratory and exhaled air was collected in a fluted mixing box. Expiratory gas drawn from the mixing box was analyzed for carbon dioxide and oxygen content by MMC Horizons metabolic cart (Sensormedics, USA). Ventilation was determined with a pneumotach integral to the metabolic cart. Esophageal temperature and ventilation were recorded at 15-s intervals and skin temperatures were recorded at 30-s intervals. Values were expressed at 1-min intervals.

Protocol

The protocol involved two sessions using the same incremental exercise on a mechanically braked cycle ergometer (Monark, Sweden). Each experimental trial occurred at the same time of day and followed a 24-hour period without heavy or prolonged physical activity. The cycle ergometer power was increased by 40 W every 2 min. This continued until the subject could no longer maintain the prescribed cadence of 80 rpm or if the subject's rate of oxygen consumption ceased to increase. The average number of days between trials was 5.9 ± 2.1 days.

Analysis and Statistics

Tidal volume, frequency of respiration, and the ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) were plotted as a function of esophageal temperature. Esophageal temperature thresholds (31, 32) for the ventilatory equivalents were independently determined from these graphs by two observers and, in the case of a discrepancy, a third observer was used. Mean esophageal temperature points, esophageal temperature

plateau points for V_T and mean esophageal temperature thresholds for f, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ were compared between trials using a paired, two-tailed Student's t-test (SPSS v. 10, Chicago, Ill., USA). Reproducibility of individual esophageal temperature thresholds for f, $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ and individual esophageal temperature plateau points for V_T was assessed with between-trial scatter plots. The slope of the best-fit linear regression equation in these scatterplots was compared to the line of identity and univariate intraclass correlation coefficients (R) were calculated between trials for each of these four (f, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, and V_T) variables. The level of significance was set at $p< 0.05$ for all statistical tests.

RESULTS

Esophageal temperature as a function of time followed a three-phase response during the exercise protocol. At the beginning of the exercise protocol the T_{es} in the two trials displayed a small initial decrease of about 0.2°C from the resting value of 36.89±0.09°C. Next there was a gradual and consistent increase in T_{es} until approximately five minutes. Finally, T_{es}

rose at a faster rate until the end of the exercise, to a value of approximately 37.8°C. The T_{es} followed a similar profile of increase in each trial and values were not significantly different between trials.

Figure 3-1 is a sample plot from one subject and it illustrates the typical responses of f and V_T as a function of T_{es}. The main V_T increase was during the first few tenths of a degree increase in T_{es}, however, after this initial response, during a localized range of T_{es}, tidal volume ceased to increase. This localized region of T_{es} was labeled the V_T plateau point as indicated by an arrow in the top panel of Figure 3-1. Frequency of respiration followed approximately the inverse pattern to V_T. Initially there was little increase in f for approximately 1.0°C increase in T_{es}. After this initial range of T_{es}, a threshold was reached and f increased as an approximately linear function of T_{es}. The mean T_{es} plateau point for V_T in Trial 1 of 37.26 ± 0.16°C was not significantly different than the mean T_{es} plateau point in Trial 2 of 37.17 ± 0.13°C (Table 3-1). The mean T_{es} threshold f in Trial 1 of 37.37 ± 0.14°C and in Trial 2 of 37.46 ± 0.17°C were also not significantly different between trials (Table 3-1). The mean,

two-trial pooled T_{es} plateau point for V_T of 37.22 ± 0.10°C and the mean two-trial pooled T_{es} threshold for f of 37.42 ± 0.11°C were also not significantly different from each other. The pooled data from the two trials for V_T and f responses as a function of T_{es} appear in Figure 3-2.

A sample subject's plots of $\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ each as a function of T_{es} are given in Figure 3-3. There was initially no change in both ventilatory equivalents until a threshold T_{es}, at which point these values increased in proportion to T_{es} until the end of the exercise. Individual and mean esophageal temperature thresholds for the ventilatory equivalents are given in Table 3-2. Both the T_{es} mean thresholds for $\dot{V}_E/\dot{V}O_2$ between trials and the mean T_{es} thresholds for $\dot{V}_E/\dot{V}CO_2$ between trials were not significantly different. The pooled, two-trial mean of the T_{es} threshold points for $\dot{V}_E/\dot{V}O_2$ of 37.49 ± 0.11°C and for $\dot{V}_E/\dot{V}CO_2$ of 37.52 ± 0.12°C were also not significantly different.

Reproducibility plots of T_{es} plateau points for V_T and for the T_{es} thresholds for f are given in Figure 3-4 and for the T_{es} thresholds ventilatory

equivalents in Figure 3-5. All intraclass correlation coefficients between trials were significant ($p < 0.05$) and the slopes in the two plots were not significantly different from the line of identity. The intraclass correlations between the T_{es} plateau points in the two trials for V_T was 0.93. The intraclass correlation between the T_{es} thresholds for f was 0.84, for $\dot{V}_E/\dot{V}O_2$ was 0.91, and for $\dot{V}_E/CO_2$ was 0.88.

DISCUSSION

The present study has two main new findings. The first is that during progressively increasing exercise intensity the increases in ventilation at lower T_{es} were due to increases in V_T and at higher T_{es} further increases in ventilation were due to increases in f. These relationships between the components of ventilation and T_{es} were shown to be reproducible (Fig 3-4, Table 3-1). The second main finding in this study was that T_{es} thresholds for ventilatory equivalents were also reproducible in these conditions (Fig 3-5, Table 3-2). The T_{es} thresholds for the ventilatory equivalents were first demonstrated by White and Cabanac (31, 32), but it was unknown if these relationships were reproducible. Together these two findings strengthen the

hypothesis that core temperature is a stimulus to ventilation during the actively induced hyperthermia of exercise.

There has been little study of the effects of actively induced hyperthermia on V_T and f (7, 17, 25, 26). The studies that exist were for sub-maximal (~ 50 to 70 % of maximal work capacities), steady state, prolonged exercise (7, 17, 25, 26). The results from these sub-maximal studies still support the present results (Fig 3-2) since at higher body temperatures and levels of ventilation, the increases in ventilation were accounted for by increases in f (7, 17, 25, 26) as reported in the present study (Fig 3-2). This is in contrast to some studies of passively induced hyperthermia where the increase in ventilation at elevated core temperatures was accounted by an increased tidal volume (V_T) with a normal f (3, 11). Despite these results (3, 11), passive body warming has also been reported to induce rapid, shallow breathing with elevated f and decreased V_T (17, 25). The reasons for the differences in the pattern of ventilation during passive body warming remain to be resolved.

Many of the previous studies of passively and exercise induced body warming and ventilation (4, 5, 17, 24, 25) have used rectal temperatures as an index of body core temperature. This has brought these results into question since rectal temperature is a poor index of both central blood (14, 16) and cranial temperatures (16). Esophageal temperature (T_{es}) has been shown to be a good index of central blood body temperature (14) and a reasonable index of cranial temperatures (15). Future studies will examine if tympanic temperature, known to be an excellent index of cranial temperature (16), has a similar relationship to the components of ventilation.

CONCLUSION

The results indicate that V_T, f and the ventilatory equivalents for carbon dioxide have reproducible relationships with esophageal temperature during progressive exercise to maximal attainable levels. At a reproducible, esophageal temperature, ventilation increase switches from being primarily due to tidal volume to being dependent on the frequency of respiration. The ventilatory equivalents for oxygen and carbon dioxide show a profile of slow increase until after a threshold point, at which point both

equivalents increase at an augmented rate. This threshold is the same for both ventilatory equivalents and it is reproducible.

Table 3-1: Individual and mean (±SE) esophageal temperature (T_{es}, °C) thresholds for frequency of respiration (f) and tidal volume (V_T) plateau points from plots of f and V_T as a function T_{es} during seated incremental cycle ergometer exercise to the point of exhaustion

	T_{es} Thresholds for f		T_{es} Plateau Points for V_T	
Subject #	Trial 1	Trial 2	Trial 1	Trial 2
1	36.94	36.62	36.89	36.62
2	36.94	37.42	36.83	36.99
3	37.12	37.25	36.99	36.99
4	37.64	37.86	37.75	37.64
5	37.86	37.59	37.91	37.48
6	37.62	38.00	37.05	37.10
7	37.48	37.48	37.42	37.37
Mean±SE	37.37 ± 0.14	37.46 ± 0.17	37.26 ± 0.16	37.17 ± 0.13
	•-------NS-------•		•-------NS-------•	
Two Trial Mean±SE	37.42 ± 0.11°C		37.22 ± 0.10°C	
	•----------NS----------•			

Table 3-2: Individual and mean (±SE) esophageal temperature (T_{es}, °C) thresholds for ventilatory equivalents for oxygen consumption and carbon dioxide production. Thresholds were taken from plots of the ventilatory equivalents as a function of T_{es} during incremental seated cycle ergometer exercise to the point of exhaustion

	Thresholds for $\dot{V}_E/\dot{V}O_2$		Thresholds for $\dot{V}_E/\dot{V}CO_2$	
Subject #	Trial 1	Trial 2	Trial 1	Trial 2
1	36.85	36.70	36.95	36.60
2	37.00	37.30	37.00	37.30
3	37.40	37.45	37.50	37.45
4	37.80	37.90	37.80	37.90
5	38.00	37.70	38.10	37.70
6	37.60	38.00	37.70	38.10
7	37.60	37.55	37.60	37.55
Mean±SE	37.46 ± 0.12	37.51 ± 0.09	37.52 ± 0.13	37.51 ± 0.10
	•-------NS-------•		•-------NS-------•	
Two Trial Mean±SE	37.49 ± 0.11°C		37.52 ± 0.12°C	
	•----------NS----------•			

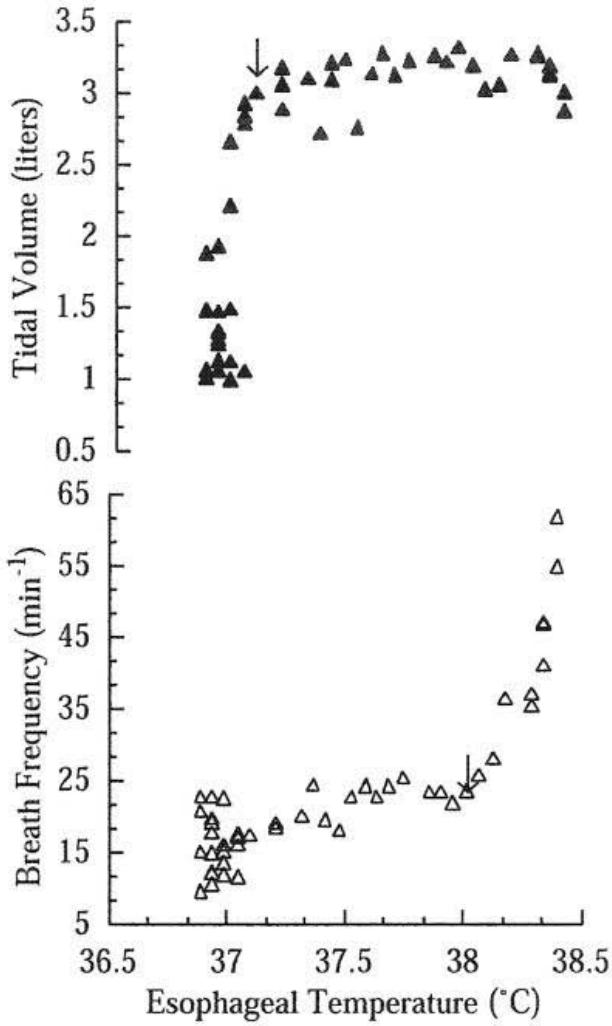

Figure 3-1: Tidal volume (V_T) and frequency of respiration (f) plotted as a function of esophageal temperature (T_{es}) for a sample subject during incremental seated cycle ergometer exercise to the point of exhaustion. In the top panel of the figure the arrow illustrates the T_{es} at the V_T plateau point, in the bottom panel the arrow illustrates the T_{es} threshold for elevated f.

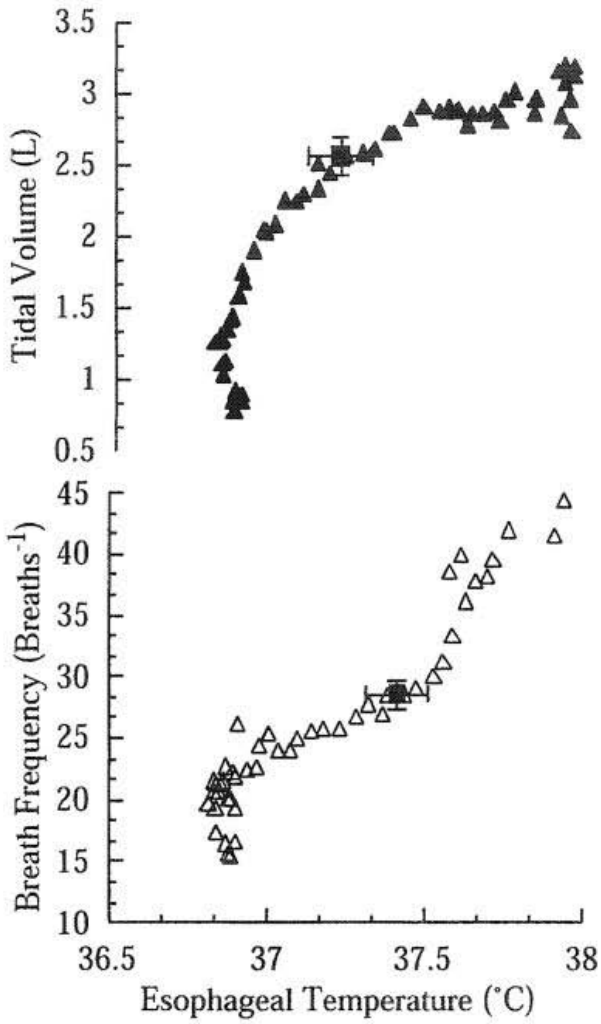

Figure 3-2: Mean tidal volume (V_T) and frequency of respiration (f) expressed as a function of their esophageal temperatures (T_{es}) during incremental seated cycle exercise to the point of exhaustion. Indicated in the figure are the mean (±SE) esophageal temperatures at the mean V_T plateau point and the mean f threshold.

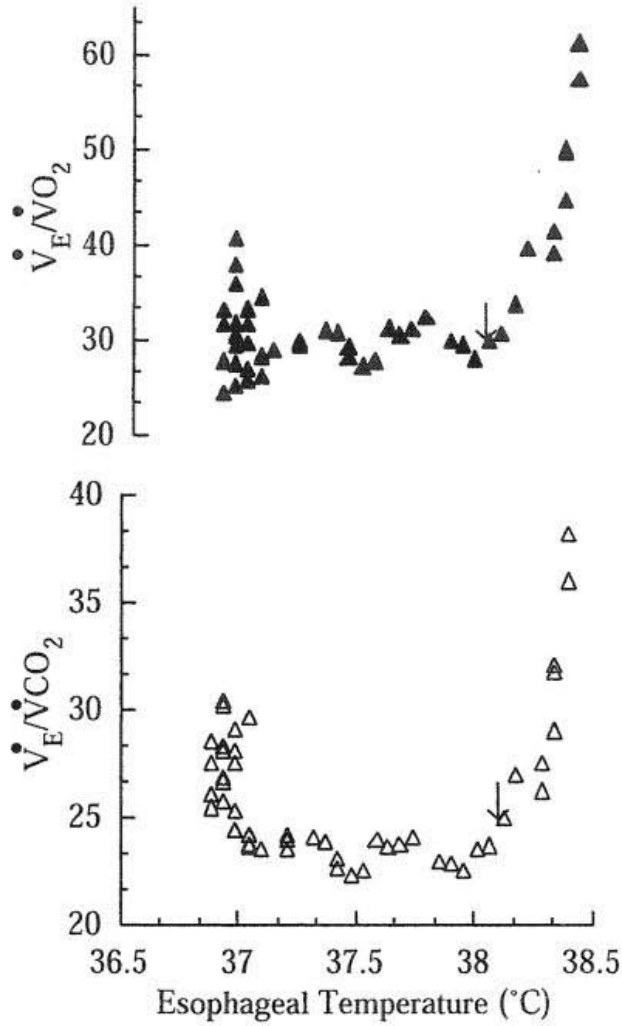

Figure 3-3: Ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$) and the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) plotted as a function of esophageal temperature (T_{es}) for a sample subject during incremental seated cycle ergometer exercise to the point of exhaustion. In the top panel of the figure the arrow illustrates the T_{es} at the $\dot{V}_E/\dot{V}O_2$ threshold point, in the bottom panel the arrow illustrates the T_{es} threshold for $\dot{V}_E/\dot{V}CO_2$.

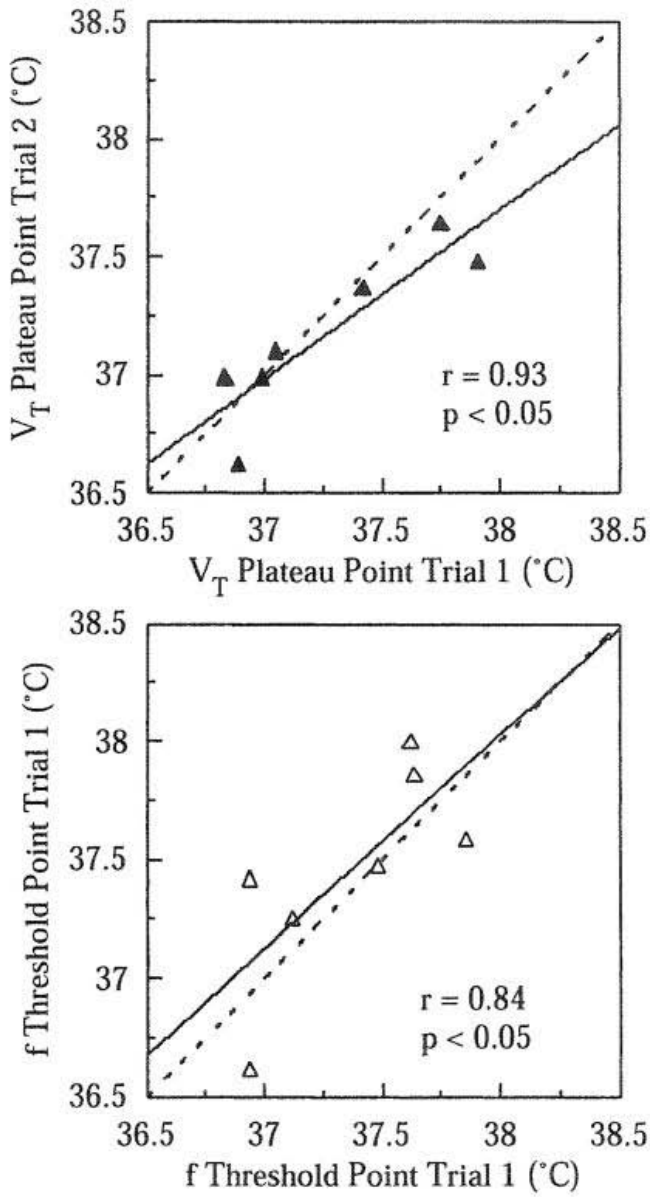

Figure 3-4: Reproducibility of the esophageal temperature (T_{es}) at the tidal volume plateau point and at the point of elevated frequency of respiration during incremental exercise to the point of exhaustion. The dotted line is the line of identity and the solid line is the best fit line.

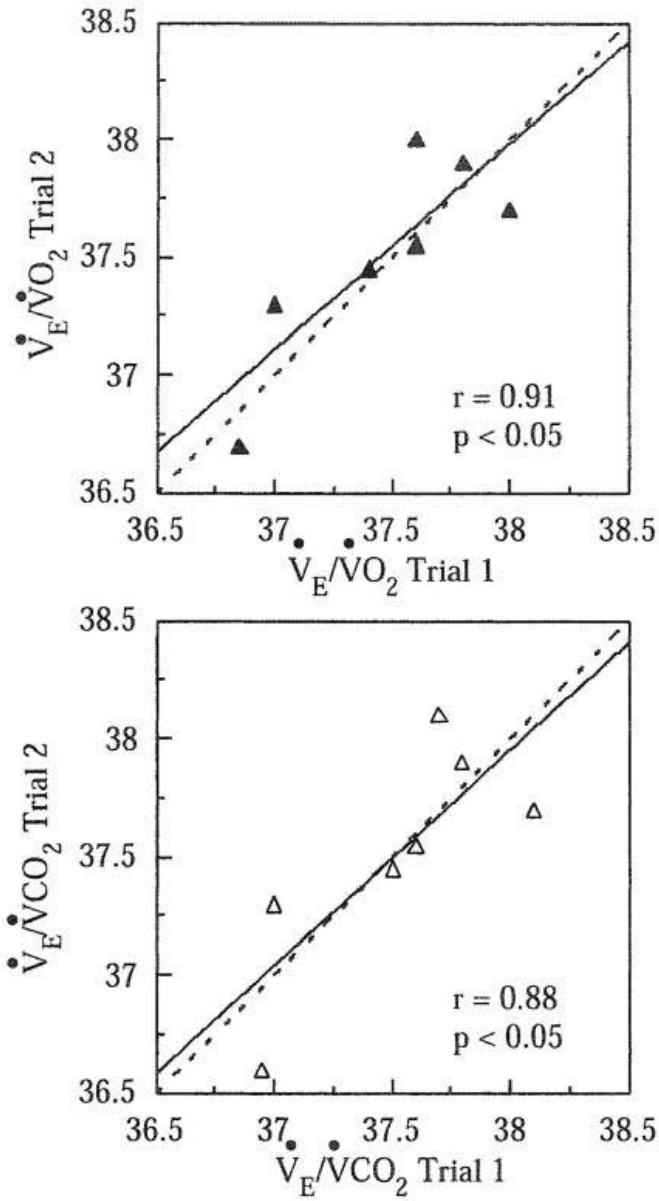

Figure 3-5: Reproducibility of the esophageal temperature (T_{es}) at the ventilatory equivalent for oxygen threshold point and the ventilatory equivalent for carbon dioxide threshold point during incremental exercise to the point of exhaustion. The dotted line is the line of identity and the solid line is the best fit line.

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Changes in the Ventilation Response to Carbon Dioxide Following Exercise Induced Hyperthermia in Humans

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Introduction

At rest, arterial carbon dioxide (Pa_{CO_2}) is a dominant mediator of human ventilation ($\dot{V}_E$) as evidenced by small elevations in the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) inducing large compensatory increases in $\dot{V}_E$, at a given inspired oxygen tension (19). During human exercise ventilation increases by as much as 20 fold over resting levels (20), but the role of carbon dioxide in this $\dot{V}_E$ response has not been resolved (see (9) for a review). Despite these large increases in ventilation, human Pa_{CO_2} is either at rest levels during low to moderate exercise (18, 23) or decreased at higher levels of exercise (10, 23). A potential explanation for these large increases in ventilation, despite unchanged or decreasing levels of Pa_{CO_2}, is that there is a temperature-induced change in the sensitivity of peripheral and/or central respiratory control centers to arterial carbon dioxide levels. This follows from studies that show during passive body warming carbon dioxide sensitivity increases at higher core temperatures (1, 8).

From the studies that have assessed carbon dioxide sensitivity changes during exercise-induced hyperthermia (4-6, 12, 22, 24), either body core temperature and the degree of hyperthermia was not assessed (24), rectal temperature (5, 6, 22) was employed that does not follow core or brain temperatures in a reliable manner (14, 15) or the CO_2 breathing (5, 6, 12, 22, 24) was not preceded by a hyperventilation to allow the establishment of a central chemo-reflex threshold (4). To address these concerns we assessed core temperature using esophageal temperature that gives a more reflective change of central blood temperature (11) and examined carbon dioxide sensitivity with a Read rebreathing test (21), preceded by a hyperventilation (4), before and after subjects were rendered hyperthermic by exercise. We hypothesized that the exercise-induced elevated ventilation could be in part due to a positive interaction of Pa_{CO_2} (19) and core temperature (1, 3, 8, 13) during the hyperthermia induced by exercise. Carbon dioxide sensitivity and the central chemoreflex threshold were compared between normothermic and hyperthermic subjects to test this hypothesis.

Material and Methods

Seven men between the ages of 18 and 40 (26.6 ± 1.0 years; 74.9 ± 1.5 kg; 1.759 ± 0.006 m; mean ± SE) volunteered to perform two experimental incremental exercise sessions on a seated cycle ergometer separated by a minimum of three days. Each session was performed at about the same time of day with a maximum of a one-hour time difference between the two sessions. The ambient temperature was 23.9±0.5°C and relative humidity was 40 to 50%. The experiments were approved by an ethics committee for human experimentation at Memorial University of Newfoundland.

Measurement and Instrumentation

Pulmonary function variables and oxygen consumption were collected using a breath-by-breath Senosormedics VMAX 229c metabolic cart (Yorba Linda, California) from subjects wearing a nose clip and fitted with a mouthpiece connected to a Mass Flow Sensor™. Before all experimental sessions the flow sensor was calibrated with known syringe volumes and rates. The inhaled air directed over the mass flow sensors of the metabolic cart was controlled by two inflatable balloon valves. This allowed the

subject to be switched from breathing room air to the five liter rebreathing bag without having to remove the mouthpiece.

A gas sample was drawn from the inspired and expired air in the mass flow sensor to the metabolic cart through Permapure™ tubing for gas analysis at a rate of 500 ml/min. Carbon dioxide concentration was measured using Non-Dispersive Infrared Spectroscopy and oxygen concentration was measured using paramagnetic sensors. Gas concentrations of the expired and inspired air were also determined on a breath-by-breath basis and both gas analyzers were calibrated immediately prior to all experimental sessions. The first gas was 26% oxygen with the balance from nitrogen, the second gas was 4% CO_2, 16% O_2 and the balance from nitrogen, and the last gas was atmospheric.

Esophageal temperature was recorded from a pediatric sized (~2 mm diameter) copper-constantan thermocouple (Mon-A-Therm, St. Louis, USA) inserted in the esophagus to the level of the right ventricle (17). Skin temperatures were measured using copper-constantan thermocouples taped to the forehead, chest, and thigh. Esophageal and skin thermocouples were

connected to a National Instruments SCXI-1000 data acquisition device (Austin, Texas) and values were recorded to a spreadsheet every 5 s and expressed every 30 s using an interface module designed in the National Instruments LabView 5.1™ programming environment.

All exercise sessions were performed on an electrically braked seated cycle ergometer (Lode Excaliber, Groningen). The pedaling cadence was set to a rate of 70 revolutions per minute despite work rate being independent of pedaling frequency (30 – 120 RPM) for this cycle ergometer.

Protocol

The first exercise session was used to determine the subject's maximum attainable workload; this was used to determine the appropriate workload for use in the second session. The workload on the ergometer was increased by 20 W/min until the subject's rate of oxygen consumption reached a maximum plateau or the subject failed to maintain the prescribed pedaling cadence.

Exercise during the second session was incremented from an initial level of 20 W by 20 W/min until the steady state level was reached. The steady state was set at approximately 75% of the maximum attained workload in the first session (workload% ± SE; 73.0 ± 0.8%). This level was above the ventilatory threshold (VT_2) (16) in all trials. Subjects maintained this level until a core temperature (esophageal) of approximately 38.1°C was obtained. During exercise subjects wore two sets of full-length sweat suits (80% cotton, 20% polyester) with an approximate insulation value of ~2 clo.

The second session also involved two modified Read rebreathing (21) sessions, both before and after performing the steady state exercise. Prior to each rebreathing period, subjects were asked to hyperventilate (4) for approximately 3 min until their $P_{ET}CO_2$ reached a plateau of 2.3±0.10 kPa and at this $P_{ET}CO_2$ point rebreathing began. This hyperventilation was performed so that the central chemoreflex $P_{ET}CO_2$ threshold could be located (4). Rebreathing was implemented from a 5 L bag filled with a gas mixture consisting of 43% oxygen, 7% CO_2, and the balance from nitrogen. The bag was hidden from view to remove the possibility of visual feedback affecting

the subject's ventilation rate and/or depth. After exercise, sufficient time was allowed to elapse for the subject's $\dot{V}_E$ to come back to resting or near resting values before attempting the second rebreathing period. This typically required 4-5 min. An elevated core temperature was maintained during recovery by placing blankets around the subject. Esophageal temperature at the end of exercise was $1.47 \pm 0.03^{\circ}C$ higher then resting values of $36.67 \pm 0.03^{\circ}C$. After the 4-5 min recovery the mean elevation of T_{es} was $0.84 \pm 0.02^{\circ}C$. A sample subject's $P_{ET}CO_2$ and ventilation over the time course of the entire second session is given in Figure 4-1. A sample subject's T_{es} and skin temperatures over the time course of the protocol is given in Figure 4-2.

Analysis and Statistics

For both normothermic and hyperthermic rebreathing tests, ventilation was plotted as a dependent variable against $P_{ET}CO_2$. Quantification of the physiological response to CO_2 was obtained by determining the threshold and slope of the $\dot{V}_E$ versus $P_{ET}CO_2$ curves during the rebreathing sessions (21). The threshold was denoted as the $P_{ET}CO_2$ where $\dot{V}_E$ began to increase.

The slope was obtained from a best-fit simple regression line for the supra $P_{ET}CO_2$ threshold points. Thresholds were determined independently by two observers and a third observer was used in the case of ambiguity.

The $P_{ET}CO_2$ threshold and slope of the $\dot{V}_E$ versus $P_{ET}CO_2$ curve (i.e. CO_2 sensitivity) was determined before and after heating using paired, two-tailed Student's t-test. The level of significance was set at $p< 0.05$ for comparison of mean thresholds between the two conditions. For regression lines fit to the supra $P_{ET}CO_2$ threshold data, for 7 subjects with two-tailed hypothesis testing, a r value of greater than 0.754 is significant for a p less than 0.05.

Results

The mean maximum workload attained by the subjects during the first cycle ergometer session was 272 ± 6.6 W. From the first session, steady state workloads were specified for each individual and the mean load was 197 ± 3.5 W.

Figure 4-2 displays a sample subject's T_{es} and skin temperature values over the course of the protocol. Esophageal temperature demonstrated a consistent rise in temperature after about 13 minutes until the end of the exercise period. Figure 4-3 is a sample plot of one subject's pre- and post-warming rebreathing periods and it illustrates the typical $\dot{V}_E$ and $P_{ET}CO_2$ pattern observed in the study. The lines of best fit and $P_{ET}CO_2$ thresholds are also given on the graph.

During the second exercise session esophageal temperature increased by $1.47 \pm 0.03^{\circ}C$ from the mean resting value of $36.67 \pm 0.03^{\circ}C$. After ventilation returned to pre-exercise values, during the second CO_2 rebreathing test, T_{es} was $0.84 \pm 0.02^{\circ}C$ above resting values. Both individual $P_{ET}CO_2$ threshold points were distinct and the slopes of $\dot{V}_E$ versus $P_{ET}CO_2$ were fit to the supra $P_{ET}CO_2$ threshold data. For the regression lines fit to the supra $P_{ET}CO_2$ threshold data, high mean r^2 values were evident for the CO_2 rebreathing before ($r^2 = 0.85 \pm 0.01$) and after ($r^2 = 0.91 \pm 0.01$) exercise warming. In all trials, except one, the slope of the $\dot{V}_E$ versus $P_{ET}CO_2$ line increased from the normothermic to hyperthermic condition (Table 4-1). The

mean slope of the $\dot{V}_E$ versus $P_{ET}CO_2$ line was significantly increased ($p < 0.05$) from 15.6 ± 2.6 $L \bullet min^{-1} \bullet kPa^{-1}$ in normothermic subjects to 24.0 ± 2.4 $L \bullet min^{-1} \bullet kPa^{-1}$ in hyperthermic subjects (Figure 4-4). In all subjects following the hyperthermia induced by exercise the $P_{ET}CO_2$ threshold point decreased (Table 4-1). The mean $P_{ET}CO_2$ threshold gave a significant decrease ($p<0.05$) from 6.95 ± 0.13 kPa to 6.15 ± 0.10 kPa.

Discussion

The modified Read rebreathing technique (4) employed in this study was chosen to test the central respiratory center responses to elevated inspired carbon dioxide levels during a hyperthermia induced by exercise. The results in this study show a decreased $P_{ET}CO_2$ threshold point for ventilation during carbon dioxide rebreathing with an esophageal temperature elevated by exercise (Table 4-1). These results support the hypothesis that a lower arterial blood CO_2 level is needed to initiate a hyperventilation during exercise-induced hyperthermia and that an equivalent or lower Pa_{CO_2} may be providing an enhanced stimulus to the central respiratory control centers to increase $\dot{V}_E$. The data also revealed a

greater slope of the $\dot{V}_E$ versus $P_{ET}CO_2$ relationship, or carbon dioxide sensitivity, after the exercise-induced rise in body temperature (Table 4-1). This gives further support to the idea that the central respiratory center is responding more to a given Pa_{CO_2} in the hyperthermia induced by exercise. These results could give an indication as to why resting Pa_{CO_2} (18, 23) or lower than resting Pa_{CO_2} (10, 23) can be present during the hyperventilation which accompanies exercise.

The results in the literature that examined changes of carbon dioxide sensitivity and $P_{ET}CO_2$ thresholds during human exercise are equivocal (4-7, 12, 24). Casey, Duffin, and McAvoy(4), both before and after exercise in humans, determined $P_{ET}CO_2$ threshold and slopes by Read CO_2 rebreathing preceded by a hyperventilation. They did not obtain different slope or $P_{ET}CO_2$ threshold in the two conditions. The difference between this present study and Casey et al. is probably due to the lower intensity of the exercise they employed and the possible lack of hyperthermia in their subjects. Their subject's body temperatures were not measured or maintained following exercise so the level of hyperthermia in their subjects was not documented.

We have shown previously that ventilation increases in direct proportion to core temperatures after an elevation of core temperature of ~1.0°C (3, 25). From the present results, with an increase of T_{es} of ~0.8°C during the hyperthermic CO_2 rebreathing, it would appear that approximately this core temperature increase is needed prior to the positive interaction of carbon dioxide and core temperature on ventilation becoming evident.

For studies that have measured core temperature during exercise, with elevated inspired levels of CO_2 to assess changes in carbon dioxide sensitivity, rectal temperatures were employed (5, 6, 22). Rectal temperature is an inherently slow responding core temperature (15) and is not representative of central blood or cranial temperatures (14, 15). This would appear to explain why some of these studies, during exercise, showed an increased sensitivity of human ventilation to elevated inspired CO_2 (5, 7), while other exercise studies did not shown any changes to human ventilation inspired with elevated CO_2 levels (6, 12, 24).

The $P_{ET}CO_2$ thresholds in this study were obtained with a breath-by-breath analysis while the subject performed the Read rebreathing test (21).

This was preceded by a hyperventilation (4) to allow from below-threshold to supra-threshold $P_{ET}CO_2$ levels to be observed and this allowed detection of the $P_{ET}CO_2$ threshold for ventilation. As such, the hyperventilation prior to each rebreathing period decreased the Pa_{CO_2} below the $P_{ET}CO_2$ threshold level. All previous exercise studies, except that by Casey et al (4), have estimated $P_{ET}CO_2$ thresholds during exercise with elevated inspired CO2 levels (6, 7, 12, 24). Since their subjects did not hyperventilate prior to the CO_2 rebreathing their $P_{ET}CO_2$ thresholds are only estimates and would be difficult to compare to the present results.

When the present results are compared to other hyperoxic CO_2 rebreathing studies, but during passive warm bath-induced rather than exercise-induced increases in core temperature, a similar increased sensitivity of ventilation to inspired carbon dioxide levels (1, 8, 13, 22) is evident. For studies with passively induced hyperthermia, that preceded (1, 13) the hyperoxic CO_2 rebreathing with a hyperventilation, no change in $P_{ET}CO_2$ thresholds were evident. The reason for this difference is not clear but may suggest that a post-exercise metabolite could be contributing to the

responses in the present study. For previous researchers who found a change in the $P_{ET}CO_2$ threshold (6, 8) during passively induced hyperthermia, this may have been because they extrapolated from supra-threshold data points therefore failing to account for the drive in ventilation due to the additive effect of an increased body temperature.

Core temperature having an effect on ventilation provides evidence to support the hypothesis that ventilation is a thermoregulatory effector. Some possible consequences of elevated heat loss from the upper airways include selective brain cooling (2) in hyperthermic humans. The temperature induced increases in ventilation in resting hyperthermic humans or exercising humans might be viewed as a vestigial panting response (2).

Conclusion

The results support the hypothesis that there is a positive interaction of the exercise-induced increase in core temperature and end-tidal carbon dioxide levels on human ventilation. A modified Read rebreathing (21) following hyperventilation gave a significantly lower threshold and a

significantly steeper slope between end-tidal carbon dioxide and $\dot{V}_E$ indicating that actively increased body temperature increases the sensitivity to CO_2. The results suggest that a given level of carbon dioxide during the hyperthermia of exercise would give a proportionately greater ventilation responses to that observed in the same normothermic subjects.

Table 4-1: Individual and mean (±SE) end-tidal carbon dioxide ($P_{ET}CO_2$) thresholds for ventilation ($\dot{V}_E$) and slopes of the relationship of $\dot{V}_E$ expressed as a function of $P_{ET}CO_2$ in normothermic and in hyperthermic males following cycle ergometer exercise

	$P_{ET}CO_2$ Thresholds (kPa)		CO_2 Response Slopes ($L \bullet min^{-1} \bullet kPa^{-1}$)	
Subject #	Pre-Warming	Post-Warming	Pre-Warming (R^2)	Post-Warming (R^2)
1	6.3	5.8	16.0 (0.93)	28.9 (0.92)
2	6.4	6.1	6.4 (0.78)	22.1 (0.95)
3	7.9	7.1	18.0 (0.92)	17.7 (0.91)
4	6.8	6.5	11.3 (0.83)	18.0 (0.97)
5	6.3	5.4	13.0 (0.82)	18.6 (0.81)
6	8.0	6.0	29.0 (0.95)	29.7 (0.91)
7	5.8	5.2	15.2 (0.74)	32.9 (0.92)
Mean±SE	6.8 ± 0.12	6.0 ± 0.09	15.6 ± 1.0 (0.85 ± 0.01)	24.0 ± 0.9 (0.91 ± 0.01)
	•-------*-------•		•-------*-------•	

* Significant difference $P < 0.05$

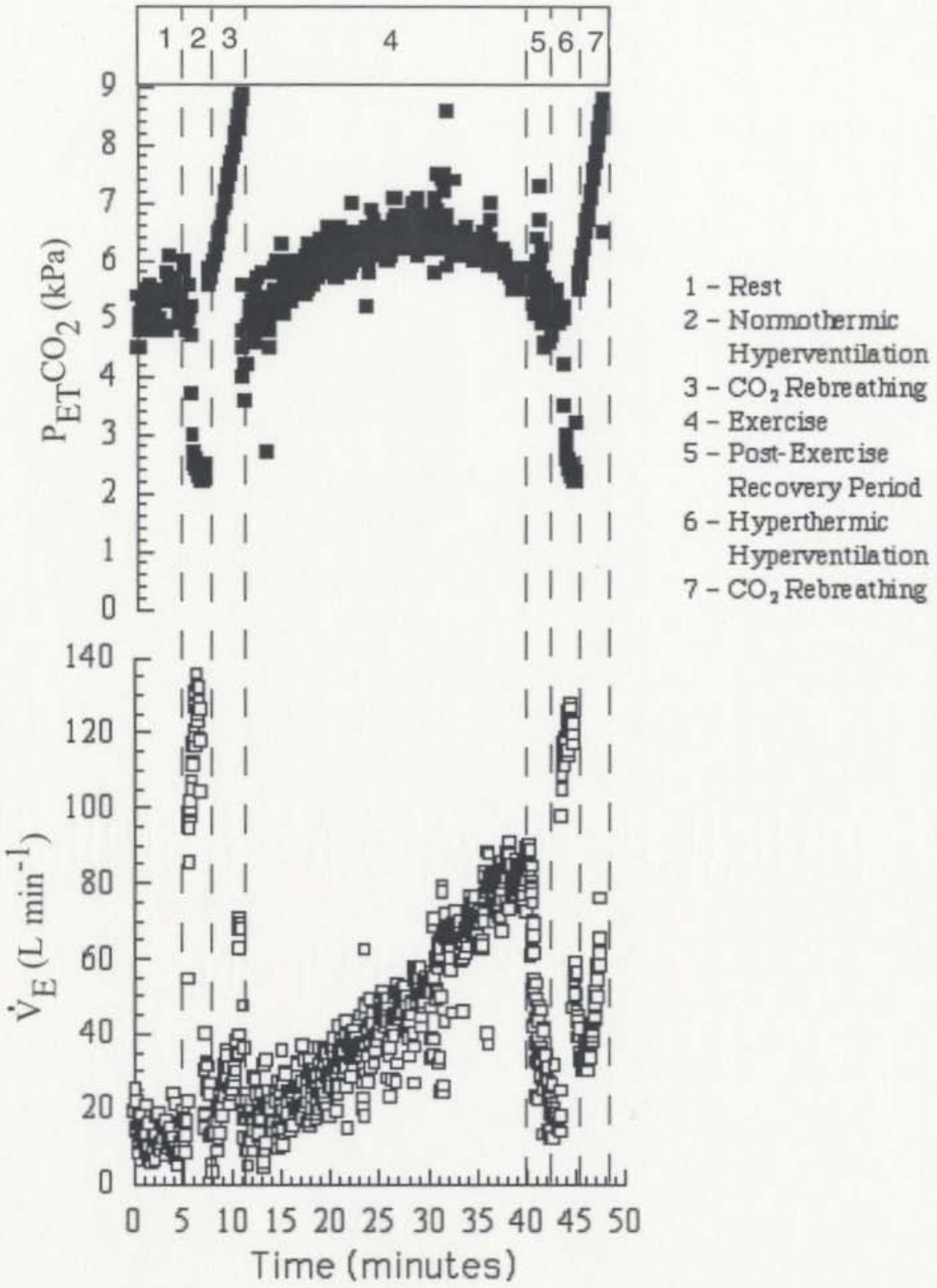

Figure 4-1: Sample subject's partial pressure of end tidal carbon dioxide and minute ventilation response expressed as a function of time across the entire protocol

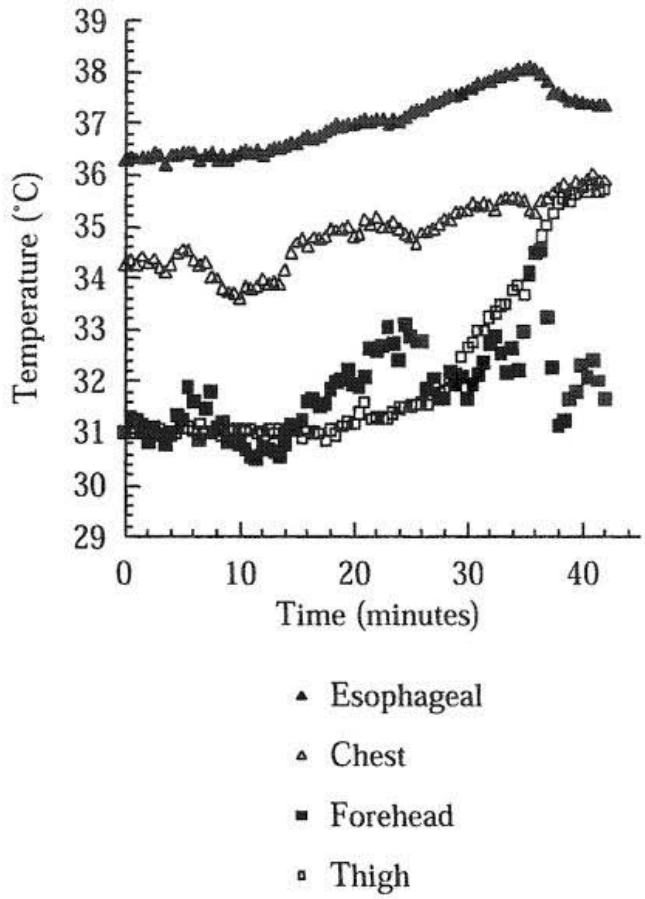

Figure 4-2: Sample subject's esophageal temperature and skin temperatures expressed as a function of time across the entire protocol

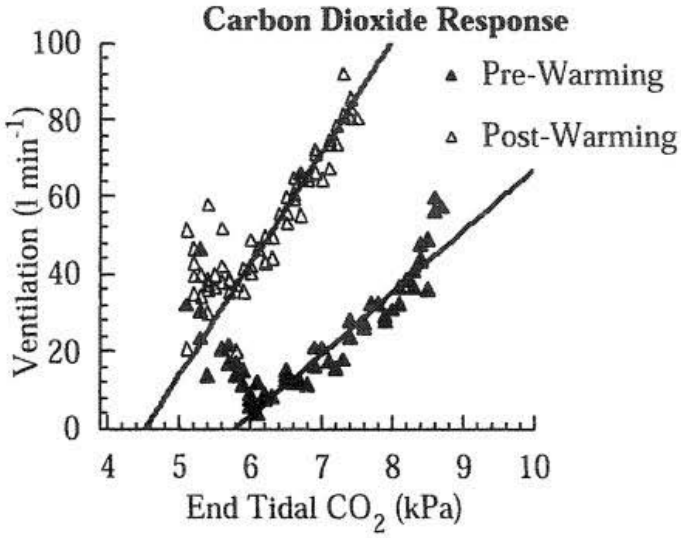

Figure 4-3: Sample subject's end tidal carbon dioxide ($P_{ET}CO_2$) threshold points and slopes of ventilation to $P_{ET}CO_2$ before and after exercise induced hyperthermia

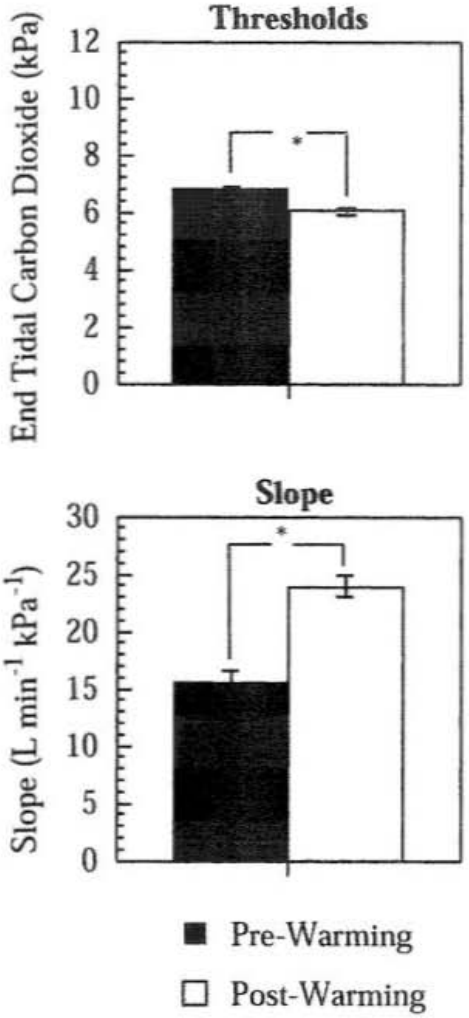

Figure 4-4: Mean end tidal carbon dioxide threshold ($P_{ET}CO_2$) points for ventilation ($\dot{V}_E$) and slopes of $\dot{V}_E$ to $P_{ET}CO_2$ before and after exercise induced hyperthermia. * indicates no significant difference ($p < 0.05$).

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Summary

This thesis explored the possible relationship between neural and metabolic mediators of human ventilation. Chapter 3, Reproducibility of the Relationships between Ventilation and Esophageal Temperature During Hyperthermia in Humans, investigates if there is a consistent relationship between temperature and ventilation. The study demonstrated that core body temperature is correlated with ventilation ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$) and with the components of $\dot{V}_E$ (V_T and f) and that these relationships are reproducible.

Having shown that there appears to be a reproducible relationship a second study was performed to assess the possibility of a cause-and-effect relationship. Specifically, the effect that body temperature has on the ventilatory response to CO_2 was studied. This venue was chosen because CO_2 is the dominant mediator of $\dot{V}_E$ at rest and it would stand to reason that it would play a dominant role in the control of $\dot{V}_E$ during exercise also. This study is chapter 4, Changes in the Ventilation Response to Carbon Dioxide Following Exercise Induced Hyperthermia in Humans.

The results of this study indicate that body temperature affects CO_2 sensitivity since the partial pressure of end tidal CO_2 ($PetCO_2$) point at which there is a rapid increase in $\dot{V}_E$ was lowered during carbon dioxide rebreathing. The results support the hypothesis that carbon dioxide begins to affect $\dot{V}_E$ at lower partial pressures during actively induced hyperthermia. Also, after this $P_{ET}CO_2$threshold, an increase in $P_{ET}CO_2$ has a greater effect on $\dot{V}_E$ after body warming then before a body temperature increase of about 0.8°C. In summary, an increased core temperature causes $P_{ET}CO_2$ to have an earlier and more pronounced effect on $\dot{V}_E$.

The effect of body temperature on $\dot{V}_E$ has various implications. One such implication is that it supports the idea of ventilation as a means of thermoregulation. In man, the upper respiratory tract (2) has been shown to be a site of ventilatory heat loss and this may contribute to selective brain cooling and cranial temperature regulation in hyperthermic humans (1).

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